[JP,01/060803,A1(2001)]

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FULL CONTENTS CLAIM + DETAILED DESCRIPTION WRITTEN AMENDMENT

[Translation done.]

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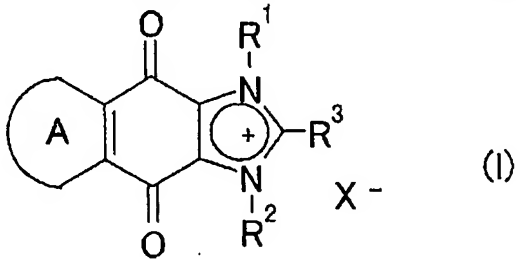
FULL CONTENTS

[Claim(s)]
[Claim 1] The condensation imidazolium inductor shown with a following general formula (I).



(I)

(The sign in a formula shows a following meaning.)
R1 and R2 : It is the same or different and - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (Low-grade alkynyl which has one or more substituents chosen from B group) - RinD, - low-grade alkyl, - low-grade ARUKENIRU, or - low-grade alkynyl, Either [at least] R1 or R2 However, - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (Low-grade alkynyl which has one or

more substituents chosen from B group) - Or - (5 which may have one or more substituents, or 7 member saturation heterocycle), (Cycloalkyl which has one or more substituents) B group : -ORa, -SRa, OH formed into - prodrug, the -O-low-grade alkylene ORa, - The O-low-grade alkylene O-low-grade alkylene ORa, the -O-low-grade alkylene NRaRb - The O-low-grade alkylene O-low-grade alkylene NRaRb, the -O-low-grade alkylene NRc-low-grade alkylene NRaRb, -OCO-NRaRb, -SORa, -SO2Ra, -SO2NRaRb, -NRa-SO2Rb, -CO2H, - The NRaRb and -NRc-low-grade alkylene NRaRb, -N(-low-grade alkylene NRaRb)2, -RinD, - NO2, -CN, - halogen, -CO2Ra, -COO-, -CONRaRb, - CONRa-O-Rb, -NRa-CORb, -NRa-CO-NRbRc, - OCORa and -CO-Ra Ra, Rb, and Rc : Are the same or different. - H, - low-grade alkyl, the - low-grade alkylene RinD, or -RinD, RinD: - (5 which may have one or more substituents, or 7 member saturation heterocycle), - - (cyclo ARUKENIRU which may have one or more substituents), (Cycloalkyl which may have one or more substituents) - Or - (heteroaryl which may have one or more substituents), (Aryl which may have one or more substituents) R3:-H -- or (low-grade alkyl which may have one or more substituents) -- or -- the low-grade alkylene of carbon numbers 2 to 5 which R2 and R3 are united and may be interrupted for O, S, or NR4 (R4:-H or - low-grade alkyl) may be formed A ring: -- the heteroaryl ring which may have the aryl ring which may have one or more substituents, or one or more substituents -- and -- When X-:counter anion, however substituent-COO- and imidazolium ion of B group form inner salt, X- does not exist.

However, R1 and R2 remove the compound which are the following combination.

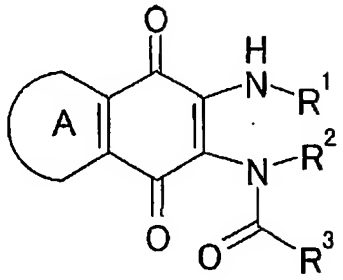
(1) One side is - low-grade alkylene (aryl which may have one or more substituents). Another side is -CH3, -(CH2) 3CH3, or - phenyl. (2) one side is - low-grade alkylene CO- (aryl which may have one or more substituents). another side -(CH2) 2CH(CH3)2 or -(CH2) 3CH3 -- or -- (3) R1 and R2 -- both - benzyl and -(CH2) 2OC2H5 or -(CH2) 2 O-COCH3.

[Claim 2] Either [at least] R1 or R2 - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (Low-grade alkynyl which has one or more substituents chosen from B group) - (Cycloalkyl which has one or more substituents chosen from C group) [or a -(5 which may have one or more substituents chosen from C group, or 7 member saturation heterocycle);C group] - Low-grade alkyl and - halogen, - halogeno low-grade alkyl, -ORa, - The O-low-grade alkylene ORa, -SRa, -NRaRb, -NO2, -CN, - CO2Ra, -CO-NRaRb, -CORa, -NRa-CORb, - The SO2NRaRb and - low-grade alkylene NRaRb, - aryl, Low-grade alkylene aryl and -OCO-Ra;RinD - - (5 which may have one or more substituents chosen from C group, or 7 member saturation heterocycle), - (Cycloalkyl which may have one or more substituents chosen from C group) - (cyclo ARUKENIRU which may have one or more substituents chosen from C group), - (Aryl which may have one or more substituents chosen from C group) [-(heteroaryl which may have one or more substituents chosen from C group);R3 / or] - H -- or (low-grade alkyl which may have one or more substituents chosen from B group) Or R2 and R3 are united and you may be interrupted by O, S, or NR4. The condensation imidazolium inductor of the claim 1 description which is the heteroaryl ring which may have one or more substituents chosen from the aryl ring or C group which may have one or more substituents as which the low-grade alkylene of carbon numbers 2 to 5 may be formed in, and;A ring is chosen from C group.

[Claim 3] Low-grade alkyl;R3 in which either [at least] R1 or R2 have one or more substituents chosen from B group [a methyl group;A ring] Benzene ring which may have one or more substituents chosen from C group, Or the thiophene which may have one or more substituents chosen from C group, The condensation imidazolium inductor of the claim 2 description which is the heteroaryl ring chosen from furan, a pyrrole, imidazole, oxazole, thiazole, a pyridine, pyrazine, pyridazine, and a pyrimidine ring.

[Claim 4] Either [at least] R1 or R2 -ORa, -NRaRb, -NRa-CORb, - The O-low-grade alkylene ORa, the -O-low-grade alkylene O-low-grade alkylene ORa, - SRa, -CONRaRb, -CN, - (cycloalkyl which may have one or more substituents

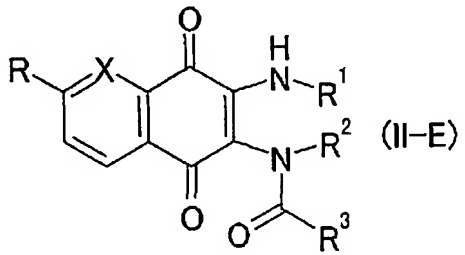
chosen from C group), - (5 which may have one or more substituents chosen from C group, or 7 member saturation heterocycle) (- even if it has one or more substituents chosen from C group) The claim 2 or the condensation imidazolium inductor given in three which is low-grade alkyl which has one or more substituents chosen from the group which consists of good aryl and good - (heteroaryl which may have one or more substituents chosen from C group).
[Claim 5] either [at least] R1 or R2 - (you may have one or more substituents chosen from C group --) The heteroaryl chosen from pyridyl, pyrazinyl one, and a pyrimidinyl group, - The claim 2 or the condensation imidazolium inductor given in three which is low-grade alkyl which has one substituent chosen from the group which consists of O-low-grade alkylene O-low-grade alkyl and -O-low-grade alkyl, and is benzene ring by which A ring may be replaced by -NO2.
[Claim 6] The 1-[(6-chloro 3-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, 1, the 2-dimethyl 4, 9-dioxo 3-[(2-tetrahydrofuranyl) methyl]-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, 1, the 3-bis(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 1-(2-pyrazinyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-[3-(1H-4-imidazolyl) propyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, 3-(2-methoxy ethyl)-2-methyl 1-[(5-methyl 2-pyrazinyl) methyl]-4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 2-methyl 4, 9-dioxo 1, 3-bis(2-pyrazinyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-[2-(2-methoxyethoxy) ethyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-{2-[2-(2-methoxyethoxy) ethoxy] ethyl}-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 3-(3-pyridyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 1-(2-pyridyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 1-(4-pyridyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-[(2-chloro 3-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-[(2-hydroxy 4-pyridyl methyl)]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 3-(2-methoxy ethyl)-1-[(6-methoxy 3-pyridyl) methyl]-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-[(2-chloro 4-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-(4-chloro benzyl)-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-(4-fluoro benzyl)-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, 1, 3-bis(2-methoxy ethyl)-2-methyl 5-nitroglycerine 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, or these . tautomers, The condensation imidazolium inductor of the claim 1 description chosen from a salt with a halogen ion.
[Claim 7] The medicine constituent containing the condensation imidazolium inductor of claim 1 description, and the carrier permitted pharmaceutically.
[Claim 8] The medicine constituent of the claim 7 description which is an anticancer agent.
[Claim 9] The 2-acylamino 3-amino 1 and 4-quinone derivative which are shown with a following general formula (II), or its salt.



(II)

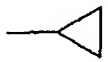
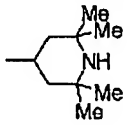
(The sign in a formula shows a following meaning.)
R1 and R2 : It is the same or different and - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (Low-grade alkynyl which has one or more substituents chosen from B group) - RinD, - low-grade alkyl, - low-grade ARUKENIRU, or - low-grade alkynyl, Either [at least] R1 or R2 However, - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (Low-grade alkynyl which has one or more substituents chosen from B group) - Or - (5 which may have one or more substituents, or 7 member saturation heterocycle), (Cycloalkyl which has one or more substituents) B group : -ORa, -SRa, OH formed into - prodrug, the -O-low-grade alkylene ORa, - The O-low-grade alkylene O-low-grade alkylene ORa, the -O-low-grade alkylene NRaRb - The O-low-grade alkylene O-low-grade alkylene NRaRb, the -O-low-grade alkylene NRc-low-grade alkylene NRaRb, -OCO-NRaRb, -SORa, -SO2Ra, -SO2NRaRb, -NRa-SO2Rb, -CO2H, - The NRaRb and -NRc-low-grade alkylene NRaRb, -N(-low-grade alkylene NRaRb)2, -RinD, - NO2, -CN, - halogen, -CO2Ra, -CONRaRb, - CONRa-O-Rb, -NRa-CORb, -NRa-CO-NRbRc, - OCORa and -CO-Ra Ra, Rb, and Rc : Are the same or different. - H, - low-grade alkyl, the - low-grade alkylene RinD, or -RinD, RinD: - (5 which may have one or more substituents, or 7 member saturation heterocycle), - - (cyclo ARUKENIRU which may have one or more substituents), (Cycloalkyl which may have one or more substituents) - Or - (heteroaryl which may have one or more substituents), (Aryl which may have one or more substituents) R3:-H -- or (low-grade alkyl which may have one or more substituents) Or R2 and R3 are united and you may be interrupted by O, S, or NR4 (R4:-H or - low-grade alkyl). the low-grade alkylene of carbon numbers 2 to 5 may be formed -- and -- A ring: -- heteroaryl ring which may have the aryl ring which may have one or more substituents, or one or more substituents. However, the compound of the following table is removed.

表1



(II-E)

Comp	X	R	-R1	-R2	-R3
E-1	CH	H	-Me	-CH_2-(3,4-Cl-Ph)	-Me
E-2	CH	H	-CH(Me)2	-CH_2-(3,4-Cl-Ph)	-Me

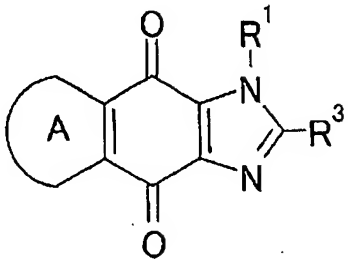
E-1	CH	H	-Me	-CH_2-(3,4-Cl-Ph)	-Me
E-2	CH	H	-$CH(Me)_2$	-CH_2-(3,4-Cl-Ph)	-Me
E-3	CH	H	-CH_2-Ph	-(4-MeO-Ph)	-Me
E-4	CH	H	-CH_2-Ph	-(3-Br-Ph)	-Me
E-5	CH	H	-CH_2-Ph	-CH_2-(4-F-Ph)	-Me
E-6	CH	H	-$(CH_2)_2$-Ph	-CH_2-(4-F-Ph)	-Me
E-7	CH	H	-$(CH_2)_2$-OH	-Me	-Me
E-8	CH	H	-$(CH_2)_2$-OH	-CH_2-Ph	-Me
E-9	CH	H	-$(CH_2)_2$-OH	-(4-MeO-Ph)	-Me
E-10	CH	H	-$(CH_2)_2$-OH	-(4-MeCO-Ph)	-Me
E-11	CH	H	-$(CH_2)_2$-OH	-(3-Br-Ph)	-Me
E-12	CH	H	-$(CH_2)_2$-Cl	-CH_2CO_2Et	-Me
E-13	CH	H	-CH(Me)-CO_2H	-Me	-Me
E-14	CH	H	-CH(Me)-CONHMe	-Me	-Me
E-15	CH	H	-CH(Me)-CONHMe	-$CH(Me)_2$	-Me
E-16	CH	H	-CH(Me)-CONHMe		-Me
E-17	CH	H	-CH(Me)-CONHMe	-Me	-$(CH_2)_2$Me
E-18	CH	H	-CH(Me)-CONHMe	-Me	-$CH(Me)_2$
E-19	CH	H	-CH(Me)-CONHOMe	-Me	-Me
E-20	N	H	-CH(Me)-CONHMe	-Me	-Me
E-21	N	Me	-CH(Me)-CONHMe	-Me	-Me
E-22	CH	H		-Me	-Me

(-- the inside of front, and Comp -- a compound number -- Me -- a methyl group -- Et -- an ethyl group -- Ph -- a phenyl group -- moreover, in the case of a substitution phenyl group, a substituent is shown with a substitution position before Ph, for example, 3 and 4-Cl-Ph shows 3 and 4-dichlorophenyl.)

[Claim 10] The 2-acylamino 3-amino 1 of claim 9 description, 4-quinone derivative or its salt, and the medicine constituent containing the carrier permitted pharmaceutically.

[Claim 11] The medicine constituent of the claim 10 description which is an anticancer agent.

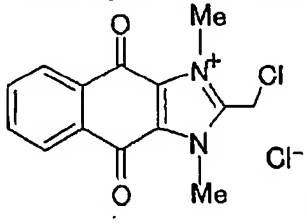
[Claim 12] The condensation imidazole derivative shown with a following general formula (III), or its salt.



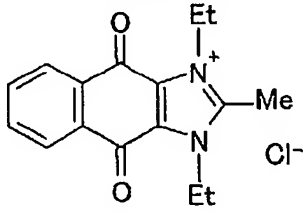
(III)

(The sign in a formula shows a following meaning.)
R1: - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - Or - (cycloalkyl which has one or more substituents), (Low-grade alkynyl which has one or more substituents chosen from B group) however, -NH2, -NMe2, -NEt2, -OH, - halogen, and - (- [Cl and]) - Remove the low-grade alkyl group which has one or more substituents chosen from the group which consists of a phenyl which may be replaced by F, -Me, or -OMe. B group : -ORa, -SRa, OH formed into - prodrug, the -O-low-grade alkylene ORa, - The O-low-grade alkylene O-low-grade alkylene ORa, the -O-low-grade alkylene NRaRb - The O-low-grade alkylene O-low-grade alkylene NRaRb, the -O-low-grade alkylene NRc-low-grade alkylene NRaRb - OCO-NRaRb, -SORa, -SO2Ra, -SO2NRaRb, - The NRa-SO2Rb, -CO2H, -NRaRb, and -NRc-low-grade alkylene NRaRb, -N(- low-grade alkylene NRaRb)2, -RinD, -NO2, -CN, - halogen, -CO2Ra, -CONRaRb, - CONRa-O-Rb, -NRa-CORb, -NRa-CO-NRbRc, - OCORa and -CO-Ra Ra, Rb, and Rc : Are the same or different. - H, - low-grade alkyl, the - low-grade alkylene RinD, or -RinD, RinD: - (5 which may have one or more substituents, or 7 member saturation heterocycle), - - (cyclo ARUKENIRU which may have one or more substituents), (Cycloalkyl which may have one or more substituents) - Or - (heteroaryl which may have one or more substituents), (Aryl which may have one or more substituents) R3:-H -- or (low-grade alkyl which may have one or more substituents) -- and -- A ring: -- heteroaryl ring which may have the aryl ring which may have one or more substituents, or one or more substituents.

[Detailed Description of the Invention]
Technical field This invention relates to medicine, a new condensation imidazolium inductor especially useful for the therapy of cancer, and its new manufacture intermediate product compound.
Background art As the aryl ring or heteroaryl ring which has antitumor activity conventionally, and the condensed imidazolium inductor 4 of ** and bottom type and 9-dioxo [2 and 3-naphth d] imidazolium compound (KP-1, KP-3 grade) is [only being indicated by Khim.Pharm.Zh, 32 (6), and 10-11 (1998) and].



(KP-1)



(KP-3)

(Et shows ethyl among a formula and Me shows methyl, respectively.) the following -- the same .

J. Med.Chem., 7 (3), and 362-364 (1964), Both R1 and R2 are low-grade alkyl, or one side is - low-grade alkylene (aryl which may have one or more substituents). The compound whose another side is -CH3, -(CH2) 3CH3, or - phenyl group, Or one side is - low-grade alkylene CO- (aryl which may have one or more substituents), and -(CH2) 2CH(CH3)2 or -(CH2) 3CH3, and the indication of a compound that comes out and has a certain antimicrobial action have another side. However, there is no indication about an anticancer operation.

Furthermore, in [J.Org.Chem.USSR, 1, 1479-85 (1965), JP,H3-258765,A, JP,H6-59371,A, etc.] the general formula (I) of after-mentioned this invention, 4 and 9-dioxo [2 and 3-naphth d] imidazolium inductor both R1 and whose R2 are low-grade alkyl groups is indicated. However, there is no indication about the medicine use of these compounds.

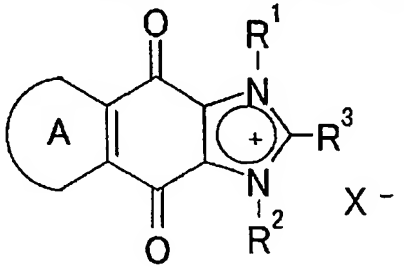
The indication of isoquinoline 5 useful as an herbicide and 8-dione inductor has useful as herbicide 1, 4-dihydro1, and 4-dioxo naphthalene inductor in the British Patent No. 1314881 gazette at Japanese patent JP,S54-25085,B, respectively. Moreover, some 1, 4-dihydro1, and 4-dioxo naphthalene inductors are Zh.Org.Khim. and 22 (8), 1736-42 (1986), J.Gen. Chem.USSR, 36,649-652 (1966), It reaches. It is well-known by a reagent catalog [Sigma Aldrich Library of Rare Chemicals Structure Index, withupdate (Aldrich Chemical Company, Inc.), etc.]. However, about the medicine use of these compounds, there is all no indication.

WO 97/No. 30022 gazette, J.Med.Chem.39, 1447-1451 (1996) and J.Med.Chem., 7 (3), and 362-364 (1964) have the indication of an aryl ring and the condensed imidazole derivative.

Indication of invention It has a good anticancer operation and is still anxious for the invention of the anticancer agent which is moreover low toxicity.

While the new aryl ring or heteroaryl ring characterized by replacing the 1st place and/or the 3rd place by the alkyl group which has a substituent as a result of this invention person's etc. taking lessons from an anticancer agent with few side reactions and inquiring wholeheartedly, and the condensed imidazolium inductor have good antitumor activity It is low toxicity and found out that it could become the large anticancer agent of a safety margin. Moreover, the 2-acylamino 3-amino 1 useful as these manufacture intermediate products, 4-quinone derivative, and a condensation imidazole derivative are found out. Furthermore, the 2-acylamino 3-amino 1 and the 4-quinone derivative itself which is this manufacture intermediate product are also what carried out the knowledge of having good antitumor action by low toxicity, and completed this invention. It is.

namely, the medicine constituent with which this invention contains the condensation imidazolium inductor shown with a following general formula (I) and the condensation imidazolium inductor concerned, and the carrier permitted pharmaceutically -- it is especially related with an anticancer agent.



(I)

(The sign in a formula shows a following meaning.)

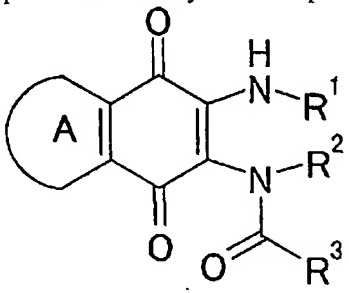
R1 and R2: It is the same or different. - (low-grade alkyl which has one or more substituents chosen from B group) - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (Low-grade alkynyl which has one or

more substituents chosen from B group) - RinD, - low-grade alkyl, - low-grade ARUKENIRU, or - low-grade alkynyl, Either [at least] R1 or R2 However, - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (Low-grade alkynyl which has one or more substituents chosen from B group) - Or - (5 which may have one or more substituents, or 7 member saturation heterocycle), (Cycloalkyl which has one or more substituents) B group : -ORa, -SRa, OH formed into - prodrug, the -O-low-grade alkylene ORa, - The O-low-grade alkylene O-low-grade alkylene ORa, the -O-low-grade alkylene NRaRb - The O-low-grade alkylene O-low-grade alkylene NRaRb, the -O-low-grade alkylene NRc-low-grade alkylene NRaRb, -OCO-NRaRb, -SORa, -SO2Ra, -SO2NRaRb, -NRa-SO2Rb, -CO2H, - The NRaRb and -NRc-low-grade alkylene NRaRb, -N(-low-grade alkylene NRaRb)2, -RinD, - NO2, -CN, - halogen, -CO2Ra, -COO-, -CONRaRb, - CONRa-O-Rb, -NRa-CORb, -NRa-CO-NRbRc, - OCORa and -CO-Ra, Ra, Rb and Rc : it is the same or different and they are -H, - low-grade alkyl, the - low-grade alkylene RinD or -RinD, and RinD:. - (even if it has one or more substituents) Good 5 or 7 member saturation heterocycle, - (cycloalkyl which may have one or more substituents), - - (aryl which may have one or more substituents), or - (heteroaryl which may have one or more substituents), (Cyclo ARUKENIRU which may have one or more substituents) R3: You may form the low-grade alkylene of carbon numbers 2 to 5 which -H, - (low-grade alkyl which may have one or more substituents), or R2 and R3 are united, and may be interrupted for O, S, or NR4 (R4:-H or - low-grade alkyl), A ring: -- the heteroaryl ring which may have the aryl ring which may have one or more substituents, or one or more substituents -- and -- When X-:counter anion, however substituent-COO- and imidazolium ion of B group form inner salt, X- does not exist.

However, R1 and R2 remove the compound which are the following combination.

(1) One side is - low-grade alkylene (even if it has one or more substituents). Are good aryl and another side -CH3, -(CH2) 3CH3, or - phenyl, One side is - low-grade alkylene CO- (aryl which may have one or more substituents), and another side (2) -(CH2) 2CH(CH3)2 or -(CH2) 3CH3, or -- (3) R1 and R2 -- both - benzyl and -(CH2) 2OC2H5 or -(CH2) 2 O-COCH3. the following -- the same .

Moreover, this invention is the manufacture intermediate product of the above-mentioned general formula (I). and the 2-acylamino 3-amino 1 and 4-quinone derivative which are shown with the following general formula (II) which has a good anticancer operation also in itself or its salt and the compound concerned or its salt, and the medicine constituent containing the carrier permitted pharmaceutically -- it is especially related with an anticancer agent.



(II)

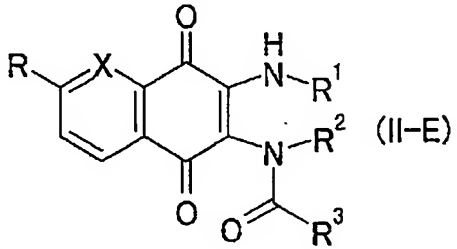
(The sign in a formula shows a following meaning.)

R1 and R2: It is the same or different. - (low-grade alkyl which has one or more substituents chosen from B group) - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (Low-grade alkynyl which has one or more substituents chosen from B group) - RinD, - low-grade alkyl, - low-grade ARUKENIRU, or - low-grade alkynyl, Either [at least] R1 or R2 However, - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-

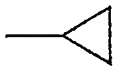
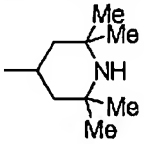
grade ARUKENIRU which has one or more substituents chosen from B group) - (Low-grade alkynyl which has one or more substituents chosen from B group) - Or - (5 which may have one or more substituents, or 7 member saturation heterocycle), (Cycloalkyl which has one or more substituents) B group : -ORa, -SRa, OH formed into - prodrug, the -O-low-grade alkylene ORa, - The O-low-grade alkylene O-low-grade alkylene ORa, the -O-low-grade alkylene NRaRb - The O-low-grade alkylene O-low-grade alkylene NRaRb, the -O-low-grade alkylene NRc-low-grade alkylene NRaRb, -OCO-NRaRb, -SORa, -SO2Ra, -SO2NRaRb, NRa-SO2Rb, -CO2H, - The NRaRb and -NRc-low-grade alkylene NRaRb, -N(-low-grade alkylene NRaRb)2, -RinD, - NO2, -CN, - halogen, -CO2Ra, -CONRaRb, - CONRa-O-Rb, -NRa-CORb, -NRa-CO-NRbRc, - OCORa and -CO-Ra, Ra, Rb and Rc : it is the same or different and they are -H, - low-grade alkyl, the - low-grade alkylene RinD or -RinD, and RinD:. - (even if it has one or more substituents) Good 5 or 7 member saturation heterocycle, - (cycloalkyl which may have one or more substituents), - - (aryl which may have one or more substituents), or - (heteroaryl which may have one or more substituents), (Cyclo ARUKENIRU which may have one or more substituents) R3: -H or - (low-grade alkyl which may have one or more substituents), Or R2 and R3 are united and you may be interrupted by O, S, or NR4 (R4:-H or - low-grade alkyl). the low-grade alkylene of carbon numbers 2 to 5 may be formed -- and -- A ring: -- heteroaryl ring which may have the aryl ring which may have one or more substituents, or one or more substituents

However, the compound of the following table is removed.

表2



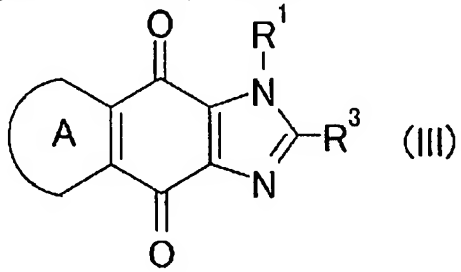
Comp	X	R	-R1	-R2	-R3
E-1	CH	H	-Me	-CH2-(3,4-Cl-Ph)	-Me
E-2	CH	H	-CH(Me)2	-CH2-(3,4-Cl-Ph)	-Me
E-3	CH	H	-CH2-Ph	-(4-MeO-Ph)	-Me
E-4	CH	H	-CH2-Ph	-(3-Br-Ph)	-Me
E-5	CH	H	-CH2-Ph	-CH2-(4-F-Ph)	-Me
E-6	CH	H	-(CH2)2-Ph	-CH2-(4-F-Ph)	-Me
E-7	CH	H	-(CH2)2-OH	-Me	-Me
E-8	CH	H	-(CH2)2-OH	-CH2-Ph	-Me
E-9	CH	H	-(CH2)2-OH	-(4-MeO-Ph)	-Me
E-10	CH	H	-(CH2)2-OH	-(4-MeCO-Ph)	-Me
E-11	CH	H	-(CH2)2-OH	-(3-Br-Ph)	-Me
E-12	CH	H	-(CH2)2-Cl	-CH2CO2Et	-Me

E-12	CH	H	-$(CH_2)_2$-Cl	-CH_2CO_2Et	-Me
E-13	CH	H	-CH(Me)-CO_2H	-Me	-Me
E-14	CH	H	-CH(Me)-CONHMe	-Me	-Me
E-15	CH	H	-CH(Me)-CONHMe	-$CH(Me)_2$	-Me
E-16	CH	H	-CH(Me)-CONHMe		-Me
E-17	CH	H	-CH(Me)-CONHMe	-Me	-$(CH_2)_2$Me
E-18	CH	H	-CH(Me)-CONHMe	-Me	-$CH(Me)_2$
E-19	CH	H	-CH(Me)-CONHOMe	-Me	-Me
E-20	N	H	-CH(Me)-CONHMe	-Me	-Me
E-21	N	Me	-CH(Me)-CONHMe	-Me	-Me
E-22	CH	H		-Me	-Me

(the inside of front, and Comp -- a compound number -- Me -- a methyl group -- Et -- an ethyl group -- Ph -- a phenyl group -- moreover, in the case of a substitution phenyl group, a substituent is shown with a substitution position before Ph, for example, 3 and 4-Cl-Ph shows 3 and 4-dichlorophenyl.) the following -- the same .

The above and the compound shown in Table 2 are literature Zh.Org.Khim. about the British Patent No. 1314881 gazette about an herbicide and Japanese patent JP,S54-25085,B, and a synthetic process, and 22 (8), 1736-42 (1986) and J.Gen. Chem.USSR, 36,649-652 (1966), [a row] It is well-known by a reagent catalog [Sigma Aldrich Library of Rare Chemicals, Structure Index, with update (Aldrich Chemical Company, Inc.), etc.].

Furthermore, this invention relates to the condensation imidazole derivative which is a new manufacture intermediate product of the above-mentioned general formula (I) and which is shown with a following general formula (III), or its salt.



(III)

(The sign in a formula shows a following meaning.)

R1: - (low-grade alkyl which has one or more substituents chosen from B group) - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - Or - (cycloalkyl which has one or more substituents), (Low-grade alkynyl

which has one or more substituents chosen from B group) however, -NH2, -NMe2, -NEt2, -OH, - halogen, and - (- [Cl and]) - Remove the low-grade alkyl group which has one or more substituents chosen from the group which consists of a phenyl which may be replaced by F, -Me, or -OMe. B group : -ORa, -SRa, OH formed into - prodrug, the -O-low-grade alkylene ORa, - The O-low-grade alkylene O-low-grade alkylene ORa, the -O-low-grade alkylene NRaRb - The O-low-grade alkylene O-low-grade alkylene NRaRb, the -O-low-grade alkylene NRc-low-grade alkylene NRaRb - OCO-NRaRb, -SORa, -SO2Ra, -SO2NRaRb, - The NRa-SO2Rb, -CO2H, -NRaRb, and -NRc-low-grade alkylene NRaRb, -N(- low-grade alkylene NRaRb)2, -RinD, -NO2, -CN, - halogen, -CO2Ra, -CONRaRb, - CONRa-O-Rb, -NRa-CORb, -NRa-CO-NRbRc, - OCORa and -CO-Ra Ra, Rb, and Rc: It is the same or different and they are -H, - low-grade alkyl, the - low-grade alkylene RinD or -RinD, and RinD:. - (5 which may have one or more substituents, or 7 member saturation heterocycle) - - (cyclo ARUKENIRU which may have one or more substituents), (Cycloalkyl which may have one or more substituents) - Or - (heteroaryl which may have one or more substituents), (Aryl which may have one or more substituents) R3: -H or - (low-grade alkyl which may have one or more substituents) A ring: Heteroaryl ring which may have the aryl ring which may have one or more substituents, or one or more substituents. the following -- the same .

A general formula (I) and the compound which (II) Reaches (III) are explained further.

The word "low-grade" Becoming means the hydrocarbon chain of the shape of a straight chain of 1-6 carbon numbers, or the letter of branching among this Description. As "low-grade alkyl", it is the alkyl group of 1 to 4 carbon numbers preferably, and they are methyl, ethyl, n-propyl, isopropyl, n-butyl, and an isobutyl machine especially preferably. As "low-grade ARUKENIRU", they are vinyl, an allyl compound, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, and 3-butenyl group preferably. As "low-grade alkynyl", they are ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, and 1-methyl 2-propynyl group preferably. Moreover, as a "low-grade alkylene", it is methylene, ethylene, trimethylene and 2, and 2-dimethyl trimethylene machine preferably.

As "aryl", an aromatic hydrocarbon ring machine is meant, and the aryl group of 6 to 14 carbon numbers is desirable, and are a phenyl, naphthyl, and a fluorenyl group preferably. Moreover, as an "aryl ring" in A ring, it is the ring which forms said aryl group, and they are benzene and a naphthalene ring preferably.

5 which contains as "heteroaryl" 1 to 4 hetero atoms chosen from N, S, and O or 6 member monocycle heteroaryl group, and these are benzene-ring or 5 to 6 member monocycle heteroaryl and condensed 2 ring type heteroaryl group, and may be saturated partially. Moreover, when N atom is included, you may form N-oxide. It is 5 to 6 member monocycle heteroaryl here, A furil, thienyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, Iso thiazolyl, oxazolyl, iso oxazolyl, oxadiazolyl, Thiadiazolyl, triazoryl, tetra-ZORIRU, pyridyl, pyrimidinyl, pilus DAJINIRU, pyrazinyl ones, and a thoriadinyl group are desirable, and as 2 ring type heteroaryl Benzofuranyl one, benzothienyl, benzothiadiazolyl, benzothiazolyl, Benzoxazolyl, benzooxadiazolyl, benzoimidazolyl, India Lil, iso India Lil, indazolyl, quinolyl, iso quinolyl, SHINNORINIRU, chinae-cortex ZORINIRU, KINOKISARINIRU, benzodioxolyl, in DORIJINIRU, and an imidazo pyridyl machine are desirable. As partial saturation heteroaryl, a 1, 2, 3, and 4-tetrahydro quinolyl machine etc. is mentioned. Furthermore, preferably, it is a furil, thienyl, imidazolyl, pyridyl, pyrazinyl one, pyrimidinyl, pilus DAJINIRU, India Lil, benzoimidazolyl, benzodioxo nil, and a quinolyl machine, and they are pyridyl, pyrazinyl one, and pyrimidinyl especially preferably.

As the heteroaryl ring in A ring It is the ring which forms ** and the above-mentioned heteroaryl group, and is 5 to 6 member monocycle heteroaryl ring preferably, and they are thiophene, Fran, a pyrrole, imidazole, oxazole, thiazole, a pyridine, pyrazine, and a pyrimidine ring still more preferably.

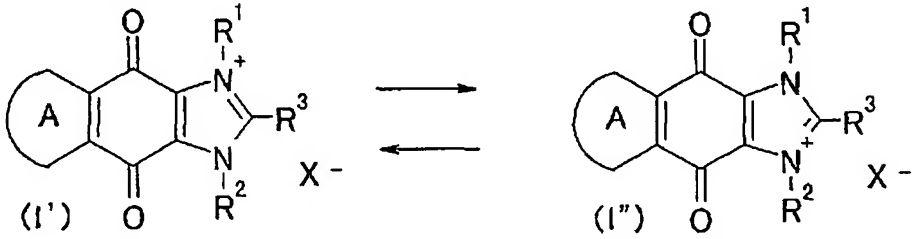
As "cycloalkyl", it is the cycloalkyl machine of 3-10 carbon numbers preferably, and they are cyclo propyl, cyclopentyl, cyclohexyl, and an adamanthyl machine especially preferably. As "cyclo ARUKENIRU", it is the cyclo alkenyl group of 3-

8 carbon numbers preferably, and they are cyclo pentenyl and a cyclohexenyl group especially preferably.
If it is anion pharmaceutically permitted as counter anion of imidazolium ion as "counter anion", there will be no restriction in particular, and they are a halogen ion and an organic-sulfonic-acid ion preferably. for example, a methansulfonic acid ion, an ethane-sulfonic-acid ion, and a benzenesulfonic acid ion -- Anion univalent [, such as acetate ions, such as a toluenesulfonic acid ion, trifluoro acetate ion, carbonate ion, and sulfate ion,] or divalent is mentioned, and it is a halogen ion especially preferably.
As "halogen", F, Cl, Br, and I atom are mentioned, and they are these ions as a "halogen ion." As "halogeno low-grade alkyl", said halogen is said low-grade alkyl replaced one or more, and is -CF3 preferably.
"5 to 7 member saturation heterocycle" is 5 containing 1 to 4 hetero atoms chosen from N, S, and O, 7 member monocycle saturation heterocycle, or its bridge ring. They are tetrahydropyranyl, tetrahydrofuranyl one, pyrrolidinyl, piperazinyl one, AZEPANIRU, JIAZEPANIRU, quinuclidinyl, piperidyl, and a mole HORINIRU machine preferably.
"OH formed into - prodrug" is the group in which the reversible prodrug inductor restored to a parent compound (hydroxy compound of a yuan) in the living body was formed, for example, is Prog.Med and a group indicated to 5:2157-2161 (1985). the low-grade alkylene COOR (the following R indicates H or low-grade alkyl to be -- the same) which may have a -OCO-substituent preferably - The low-grade alkenylene COOR which may have an OCO-substituent - The aryl, the - OCO low-grade alkylene O-low-grade alkylene COOR which may have an OCO-substituent - The low-grade alkylene COOR which may have the low-grade alkyl and -OSO2-substituent which may have OCO-CO-R and a -OCO-substituent, - O-lid RIJIRU, the 5-methyl 1, 3-dioxo ****- 2-****- 4-****- methyloxy, etc. are mentioned.
- (5 which may have one or more substituents, or 7 member saturation heterocycle) - (cycloalkyl which may have one or more substituents), - - (cyclo ARUKENIRU which may have one or more substituents), (Cycloalkyl which has one or more substituents) - (Aryl which may have one or more substituents) Or although there is no restriction in particular as a substituent in - (heteroaryl which may have one or more substituents), they are 1-4 substituents preferably chosen from following C group.
C group : - low-grade alkyl, - halogen, - halogeno low-grade alkyl, -ORa, - The O-low-grade alkylene ORa, -SRa, - NRaRb, -NO2, -CN, - The CO2Ra, -CO-NRaRb, -CORa, -NRa-CORb, -SO2NRaRb, and - low-grade alkylene NRaRb, - aryl, - low-grade alkylene aryl, and -OCO-Ra (the inside of a formula, and the meaning as the above with same Ra and Rb) It is shown.
A still more desirable group among said C group - low-grade alkyl, - halogen, - halogeno low-grade alkyl, - OH, -O-low-grade alkyl, the -O-low-grade alkylene OH, -O-low-grade alkylene O-low-grade alkyl, - Low-grade alkylene NH2, -NH2, - NH-low-grade alkyl, -N(low-grade alkyl)2, and -CO2H, -CO2-low-grade alkyl, -CO-NH2, -SO2-NH2, -NO2 And it is - CN. the following -- the same .
As a substituent in "the aryl ring which may have one or more substituents" in A ring, or "the heteroaryl ring which may have one or more substituents", preferably, the group of said C group is mentioned and a still more desirable group is the same as that of the above. It is -NO2 especially preferably.
Although there is no restriction in particular as a substituent in "the low-grade alkyl which may have one or more substituents" of R3, it is the substituent of said B group preferably, and they are - halogen, -ORa, -SRa, -NRaRb, -NO2, and -CN still more preferably.
In addition, in said B group and C group, the group Ra, Rb, and whose Rc are -H or - low-grade alkyl is more desirable as a group shown using Ra, Rb, and Rc.
Even if "R2 and R3 are united and it is interrupted by O, S, or NR4 (R4:-H or - low-grade alkyl) [form / the good low-grade alkylene" of carbon numbers 2 to 5] The low-grade alkylene chain which may be interrupted for O, S, or NR4

which R2 and R3 form (preferably) - (CH2) Mean forming 5 to 8 member heterocycle which 4-, -(CH2)2OCH2- and - (CH2) 2N(Me) CH2-, N of the both ends, and C atom are united, and is condensed with an imidazole ring.
In this invention compound (I) or (II), it is a desirable compound, Either [at least] R1 or R2 (1) - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (Low-grade alkynyl which has one or more substituents chosen from B group) - (Cycloalkyl which has one or more substituents chosen from C group) [or -(5 which may have one or more substituents chosen from C group, or 7 member saturation heterocycle);RinD] - (5 which may have one or more substituents chosen from C group, or 7 member saturation heterocycle) - (Cycloalkyl which may have one or more substituents chosen from C group) - (Cyclo ARUKENIRU which may have one or more substituents chosen from C group) - (Aryl which may have one or more substituents chosen from C group) [-(heteroaryl which may have one or more substituents chosen from C group);R3 / or] - H, - (low-grade alkyl which may have one or more substituents chosen from B group), or R2 and R3 are united, and you may be interrupted by O, S, or NR4 (R4:-H or - low-grade alkyl), Even if it forms the low-grade alkylene of carbon numbers 2 to 5 The compound which is the heteroaryl ring which may have one or more substituents chosen from the aryl ring or C group in which;A ring may have well one or more substituents chosen from C group, (2) The compound which is low-grade alkyl in which either [at least] R1 or R2 have one or more substituents chosen from B group, (3) The compound which is low-grade alkyl which has one or more substituents which both R1 and R2 are the same or different, and are chosen from B group, Either [at least] R1 or R2 (4) -ORa, -NRaRb, - The NRa-CORb and -O-low-grade alkylene ORa, the -O-low-grade alkylene O-low-grade alkylene ORa, - SRa, -CONRaRb, -CN, - (cycloalkyl which may have one or more substituents chosen from C group), - (5 which may have one or more substituents chosen from C group, or 7 member saturation heterocycle) - (Aryl which may have one or more substituents chosen from C group) And the compound which is low-grade alkyl which has one or more substituents chosen from the group which consists of - (heteroaryl which may have one or more substituents chosen from C group), (5) Either [at least] R1 or R2 are the -ORa and -O-low-grade alkylene ORa and the -O-low-grade alkylene O-low-grade alkylene ORa. - (even if it has one or more substituents chosen from C group) The compound which is low-grade alkyl which has one or more substituents chosen from the group which consists of good 5 or 7 member saturation heterocycle, - (aryl which may have one or more substituents chosen from C group), and - (heteroaryl which may have one or more substituents chosen from C group), (6) Either [at least] R1 or R2 may have one or more substituents chosen from C group. a furil, thienyl, imidazolyl, pyridyl, pyrazinyl one, and pyrimidinyl -- The compound which is low-grade alkyl replaced by the heteroaryl group chosen from pilus DAJINIRU, India Lil, benzoimidazolyl, benzodioxo nil, and a quinolyl machine, (7) Either R1 or R2 are low-grade alkyl replaced by - O-low-grade alkyl. Another side is -O-low-grade alkylene O-low-grade alkyl and -O-low-grade alkylene O-low-grade alkylene O-low-grade alkyl. - (aryl which may have one or more substituents chosen from C group) (- Even if it has one or more substituents chosen from C group) The compound which is low-grade alkyl which has one substituent chosen from the group which consists of good heteroaryl and -O-low-grade alkyl, (8) either [at least] R1 or R2 - (you may have one or more substituents chosen from C group --) The heteroaryl chosen from pyridyl, pyrazinyl one, and a pyrimidinyl group, - The compound which is low-grade alkyl which has one substituent chosen from the group which consists of O-low-grade alkylene O-low-grade alkyl and -O-low-grade alkyl, (9) The compound whose R3 is a methyl group, and (10) A rings may have one or more substituents chosen from benzene ring or C group which may have one or more substituents chosen from C group. Thiophene, Fran, a pyrrole, imidazole, oxazole, thiazole, They are the compound which is the heteroaryl ring chosen from a pyridine, pyrazine, pyridazine, and a pyrimidine ring, the compound whose (11) A rings are benzene ring which may be replaced by -NO2, or the compound whose (12) X- is a halogen ion.
Moreover, desirable compound with the another this invention compound (I), R1 and R2 are the same or different, and -

(low-grade alkyl which has one or more substituents chosen from B' group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B' group) - (Low-grade alkynyl which has one or more substituents chosen from B' group) - (Cycloalkyl which may have one or more substituents chosen from C' group) - (5 or 6 member monocycle heteroaryl which may have one or more substituents chosen from C' group) - (Aryl which may have one or more substituents chosen from C' group) - (5 or 7 member saturation heterocycle which may have one or more substituents chosen from C' group) - A low-grade alkylene (aryl which may have one or more substituents chosen from C' group), - low-grade alkylene CO- (aryl which may have one or more substituents chosen from C' group), and - either [low-grade alkyl and - low-grade ARUKENIRU or - low-grade alkynyl, however / at least] R1 or R2 - (low-grade alkyl which has one or more substituents chosen from B' group), - Or are - (low-grade alkynyl which has one or more substituents chosen from B' group), and (Low-grade ARUKENIRU which has one or more substituents chosen from B' group) [a;B' group] - ORa, -SRa, OH formed into - prodrug, the -O-low-grade alkylene RinD - SORa, -SO2Ra, -SO2NRaRb, NRa-SO2Rb, - The CO2H, -NRaRb, and - NRc-low-grade alkylene RinD, -N(- low-grade alkylene RinD)2, and -NRc-low-grade alkylene NRaRb, -N(low-grade alkylene NRaRb)2 - (even if it has one or more substituents chosen from C' group) Good 5 or 7 member saturation heterocycle, - (5 which may have one or more substituents chosen from C' group, or 6 member monocycle heteroaryl), - Cycloalkyl, the -S-low-grade alkylene RinD, -NO2, -CN, - It is CO2Ra, -CONRaRb, -NRa-CORb, -OCORa, and -CO-low-grade alkyl and -CO- (5 which may have one or more substituents chosen from C' group, or 6 member monocycle heteroaryl),;Ra, and Rb and Rc are the same or different, and it is -H, - It is low-grade alkyl or -RinD, and;RinD - (5 which may have one or more substituents chosen from C' group, or 7 member saturation heterocycle) - Or are - (5 which may have one or more substituents chosen from C' group, or 6 member monocycle heteroaryl), and (Aryl which may have one or more substituents chosen from C' group) [a;C' group] - Low-grade alkyl and - halogen, -ORa, -SRa, -NRaRb, - NO2, - CN, -CO2Ra, -CO-NRaRb, -CORa, - Are NRa-CORb and -OCO-Ra, and;R3 are -H or - low-grade alkyl, and [;A ring] - It is the condensation imidazolium inductor; and whose X- it is benzene ring which may have the substituent chosen from the group which consists of low-grade alkyl and -ORa, -NRaRb, -CN, a - halogen atom, and -NO2, and are counter anion. The inside of this invention compound (I), and especially a desirable compound, The 1-[(6-chloro 3-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, 1, the 2-dimethyl 4, 9-dioxo 3-[(2-tetrahydrofuranyl) methyl]-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, 1, the 3-bis(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 1-(2-pyrazinyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-[3-(1H-4-imidazolyl) propyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, 3- (2-methoxy ethyl)-2-methyl 1-[(5-methyl 2-pyrazinyl) methyl]-4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 2-methyl 4, 9-dioxo 1, 3-bis(2-pyrazinyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-[2-(2-methoxyethoxy) ethyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-{2-[2-(2-methoxyethoxy) ethoxy] ethyl}-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 3-(3-pyridyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 1-(2-pyridyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, 3- The (2-methoxy ethyl)-2-methyl 4, 9-dioxo 1-(4-pyridyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-[(2-chloro 3-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, 1-[(the 2-hydroxy 4-pyridyl methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3 - [IUMU and]) The 3-(2-methoxy ethyl)-1-[(6-methoxy 3-pyridyl) methyl]-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-[(2-chloro 4-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, 1- The (4-chloro benzyl)-3-(2-methoxy ethyl)-2-methyl

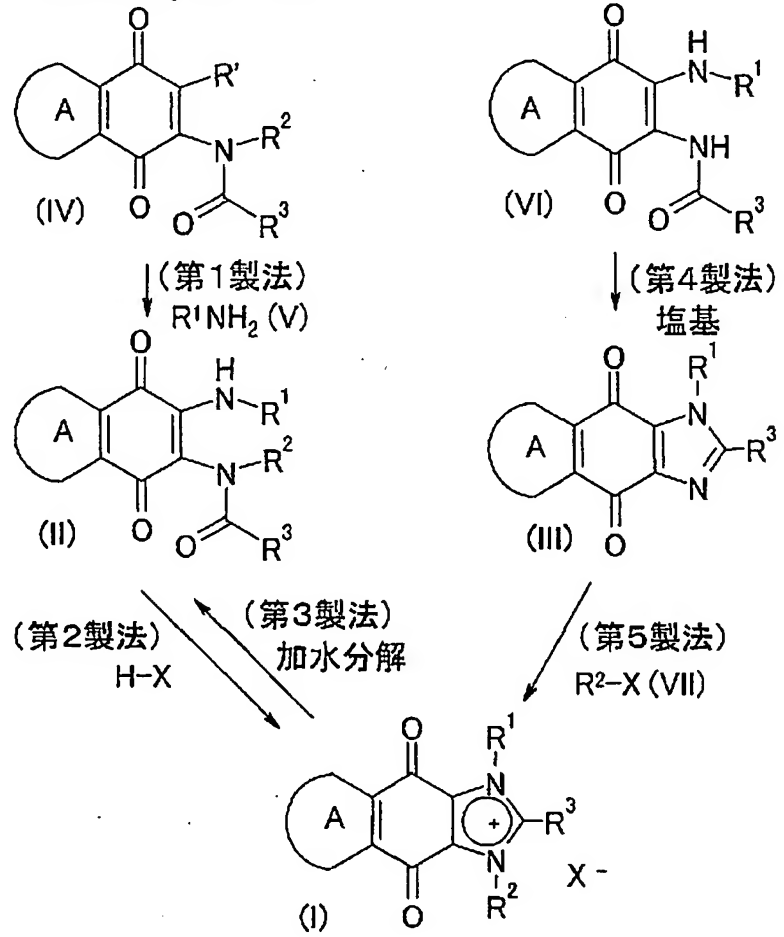
4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-(4-fluoro benzyl)-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, It is the salt of 1, 3-bis(2-methoxy ethyl)-2-methyl 5-nitroglycerine 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU or these tautomers, and a halogen ion.
The compound (I) of this invention has the tautomer shown by the bottom formula depended on delocalization of a cation, and the thing which these isomers separated, or a mixture is included by this invention. Therefore, the compound written as a 1H-imidazole 3-IUMU inductor includes the mixture of the 3H-imidazole 1-IUMU inductor which is a tautomer, and both isomers among this Description. In addition, when a compound (I) has substituent-COO- and forms imidazolium ion and inner salt, X- does not exist.



this invention compound (I) may form a salt depending on the kind of substituent in addition to a salt with said counter anion, and these salts are also included by this invention. Moreover, a salt may be formed depending on this invention compound (II) or (III) the kind of substituent, and these salts are also included by this invention. If it is the salt pharmaceutically permitted as a salt here, there will be no restriction in particular, but it is acid addition salt. On ** and a concrete target, inorganic acids, such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid, formic acid, acetic acid, a propionic acid, an oxalic acid, malonic acid, succinic acid, a fumaric acid, a maleic acid, lactic acid, a malic acid, tartaric acid, citric acid, methansulfonic acid, ethane sulfonic acid, aspartic acid, It is mentioned by acid addition salt with organic acids, such as glutamic acid, etc., and as a salt with a base Salts, ammonium salt, etc. with an organic base, such as the inorganic base containing metals, such as sodium, potassium, magnesium, calcium, and an aluminium, or monomethylamine, ethylamine, ethanolamine, lysine, and ornithine, are mentioned.
Although a geometrical isomer and a tautomer may exist depending on the kind of this invention compound (I), (II), or (III) substituent, the thing which these isomers separated, or a mixture is included by this invention. Furthermore, this invention compound may have an asymmetric carbon atom, and the isomer based on an asymmetric carbon atom may exist. This invention includes the mixture and the thing which isolated of these optical isomers. Moreover, this invention compound may form N-oxide depending on the kind of substituent, and these N-oxide objects are also included by this invention. furthermore, this invention -- this invention compound (I) and (II) -- or (III) also includes the substance of various kinds of hydrates, solvate, and crystal polymorphism.
(Manufacturing method)
It is a method, for example, J.Org.Chem.USSR, this invention compound (I), (II), and (III) given in literature, 1, and 1479-85 (1965), J. With the application of a well-known method, it can manufacture easily to a person skilled in the art, using the method indicated to Med.Chem., 7 (3), 362-364 (1964), JP,H3-258765,A, etc., and the same method.
In addition, depending on the kind of functional group, a raw material or a blocking group suitable in the stage of an intermediate product, i.e., transpose to the group which can be converted into the functional group concerned easily, may be effective on manufacture technology in the functional group concerned. The appropriate back can remove a blocking

group if needed, and a desired compound can be obtained. A hydroxyl group (such an amino group as a functional group (for example, an amino group)), a carboxyl group, etc. can be mentioned, and it is those blocking groups. The blocking group of ** (Greene), for example, Green, and the Wuts (Wuts) work, "Protective Groups in Organic Synthesis", and the 2nd-edition description can be mentioned, and what is necessary is just to use these suitably according to a reaction condition.

A typical production method is explained below.



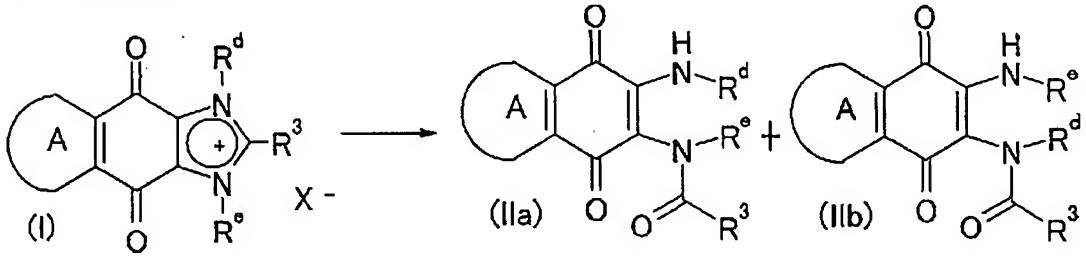
(R' means among a formula hydrogen, methoxy or a halogen group, and the acids (preferably hydrogen fluoride, hydrogen chloride, a hydrogen bromide, hydrogen iodide, methansulfonic acid, ethane sulfonic acid, etc.) with which H-X forms anion.) the following -- the same .

The 1st process this invention compound (II) can be manufactured by making amines (V) react to a compound (IV) with a conventional method. Reactions are Chem.Pharm.Bull., 44 (6), and 1181-1187 (1996), for example, Syn.Comm., 27 (12), 2143-2157 (1997), With the application of the method of a description, it can manufacture to Tetrahedron.Lett., 39 (42), 7677-7678 (1998), etc. the compound (IV) of the inside of suitable inert solvents (for example, benzene etc.), and a

reaction equivalent amount, and (V) -- again -- yes -- using inorganic bases (potassium carbonate etc.) or organic bases suitable as an acid supplement agent (triethylamine etc.) if needed using an excessive quantity of gaps or one side -- ordinary temperature or warming -- it is advantageous to carry out in the bottom.

The 2nd process With a conventional method, this invention compound (I) can manufacture this invention compound (II), cyclization and when the fourth class chlorinates. being able to perform a reaction with the application of the method of J. Org.Chem.USSR, 1, and 1479 -85 (1965) description, for example, and using a reaction equivalent amount or an excessive quantity of acids among a suitable inert solvent (for example, alcoholic solvent) -- ordinary temperature or warming -- it is advantageous to carry out in the bottom.

The 3rd process



(Rd and Re show among a formula the arbitrary groups defined as R1 and R2.) the following -- the same .

hydrolyzing this invention compound (I) with a conventional method -- two sorts of this invention compounds (IIa) -- and (IIb) it can obtain. The obtained compound can be further given to the modification reaction of a well-known group, and can also be made into the manufacture intermediate product of the desired this invention compound (I).

the hydrolysis reaction can apply the method of a description to J.Med.Chem., 7 (3), 362-364 (1964), etc., and a reaction equivalent amount or an excessive quantity of bases are used for it among water and a suitable inert solvent (for example, ethanol etc.), for example -- ordinary temperature or warming -- it is advantageous to carry out in the bottom. As a base, lithium hydroxide, sodium hydroxide, a potassium hydroxide, sodium carbonate, potassium carbonate, etc. are mentioned here.

The 4th process this invention compound (III) can be manufactured in accordance with the method indicated to J.Med. Chem., 39 (7), 1447-1451 (1996), etc. from giving a compound (VI) to ring closure under existence of bases, such as sodium hydroxide.

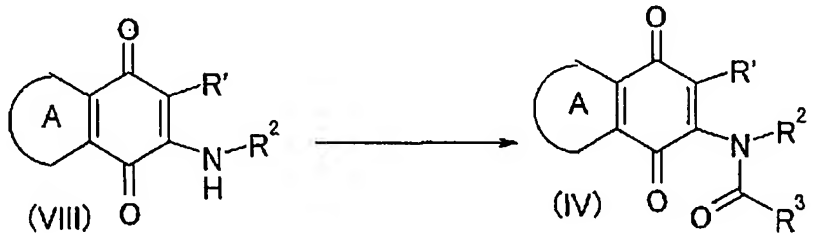
The 5th process this invention compound (I) can be manufactured by making a halide (VII) react to this invention compound (III), and considering it as the fourth class salt. a reaction can be performed with the application of the method of J.Med.Chem, 7 (3), and 362 -364 (1964) description, for example -- desirable the compound (III) of the inside of a suitable inert solvent (for example, alcoholic solvent), and a reaction equivalent amount -- and (VII) -- again -- yes -- using an excessive quantity of gaps or one side -- ordinary temperature or warming -- the bottom can carry out under the flowing-back temperature of a solvent preferably.

Other manufacturing methods this invention compound can also be manufactured by the modification reaction of the well-known substituent of versatility besides the above-mentioned process. For example, the compound which has the substituent including sulfonyl combination, N-oxide inductor of the compound which has as a substituent heteroaryl which can manufacture by oxidation reaction of a conventional method, and contains N atoms, such as a pyridyl machine, from the compound which has a sulfide bond or sulfinyl combination can be manufactured by oxidation reaction of a conventional method. The compound which has the substituent containing carboxylic acid can be manufactured by the

hydrolysis reaction of a conventional method from the compound which has ester or amide combination. The compound which has the substituent containing an amino alkyl group can be manufactured by the amination reaction of a conventional method from the compound which has halogenation alkyl combination. When it is this invention compound (II) and (III) educt, it can be considered as a salt by the salt formation reaction according to a conventional method by request.

Synthesis of a raw material compound Some raw material compounds of this invention compound are new molecular entities, and these compounds can be easily compounded like a well-known raw material compound using a well-known method to a person skilled in the art. A typical synthetic process is shown below.

Synthetic process 1



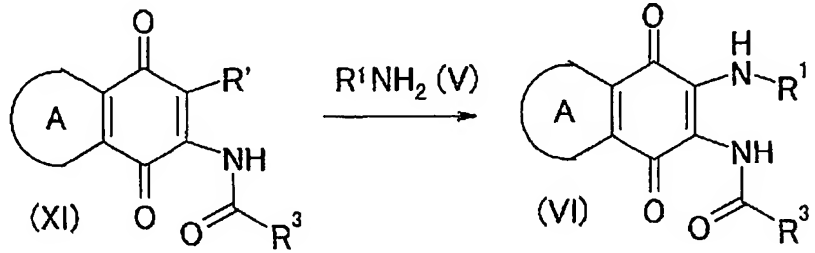
A compound (IV) can be manufactured, for example in accordance with the method indicated to J.Org.Chem.USSR, 1, 1479-85 (1965), etc. by the acylation reaction of a conventional method to which a compound (VIII) is made to react with reactant carboxylic acid, such as acid halide and an acid anhydride.

Synthetic process 2

(B1 shows among a formula the pyridine ring which may have a substituent.) the following -- the same .

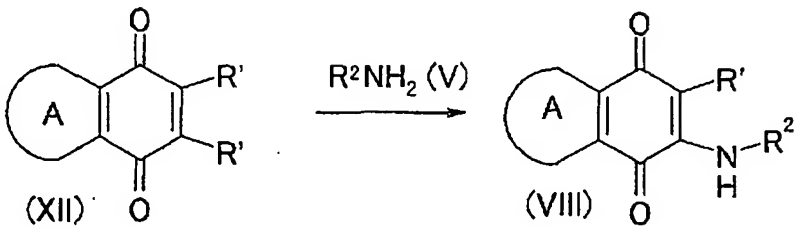
An aminomethyl pyridine inductor (X) can be manufactured by reduction of a compound (IX) in accordance with the method indicated in the German patent No. 3726993 gazette (1989) etc.

Synthetic process 3



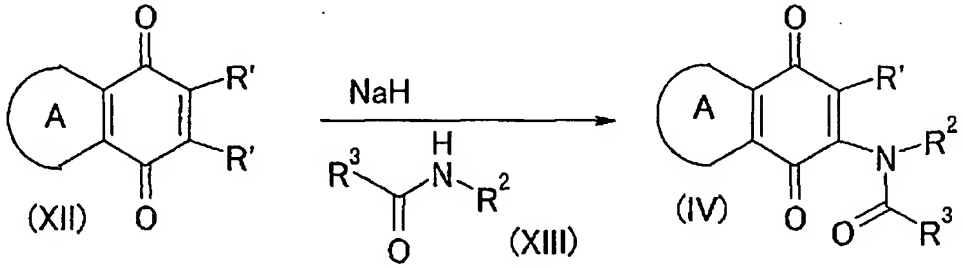
A compound (VI) can be manufactured according to amination of a compound (XI) in accordance with the method indicated to J.Med.Chem., 39 (7), 1447-1451 (1996), etc.

Synthetic process 4



Compounds (VIII) are J.Het.Chem., 33 (1), and 113-117 (1996), In accordance with the method indicated to Syn.Comm., 27 (12), 2143-2157 (1997), Tetrahedron.Lett., 39 (42), 7677-7678 (1998), etc., it can manufacture according to amination of a compound (XII).

Synthetic process 5



A compound (IV) can be manufactured by amidation of a compound (XII). A reaction uses suitable inorganic bases (NaH etc.) or organic bases (NaOMe etc.) for the compound (XIII) of a reaction equivalent amount among a suitable inert solvent (for example, N, N dimethylformamide (DMF) etc.). the reaction equivalent amount after being activated, an excessive quantity of compounds (XII) and ordinary temperature, or warming -- it is advantageous to make it react in the bottom.

Thus, isolation and refining of the manufactured this invention compound are performed by being adapted in the usual chemical operation, such as extraction, concentration, distilling off, crystallization, filtration, recrystallization, and various chromatography.

Various kinds of isomers can isolate with a conventional method using the difference of the physicochemical character between isomers. For example, racemate can be led to an isomer pure on the [method [for example,] of leading to diastereomeric salt with common optical activity acids (tartaric acid etc.), and carrying out optical resolution] solid target by a general optical resolution method. Moreover, the mixture of a diastereomer is separable with fractional-crystallization-izing or chromatography, for example. Moreover, an optical activity compound can also be manufactured by using a suitable optical activity raw material.

Industrial availability The compound (I) of this invention and (II) have good cancer cell multiplication depressant action, and, moreover, are useful as a large anticancer agent of a safety margin at low toxicity. therefore, this invention compound -- cancer -- desirable -- all the solid carcinota and a lymphoma -- it has the multiplication depressant action of tumors, such as skin carcinoma, vesical cancer, a breast cancer, a uterine cancer, an ovarian cancer, a prostatic cancer, lung cancer, colon cancer, a pancreatic cancer, a renal cancer, and gastric cancer, especially, and is useful for these therapies. in using the cancer cell growth inhibition examination and the mouse cancer-bearing model especially In a vivo cancer growth inhibition examination, it has the good antitumor activity exceeding the existing anticancer agent to two or more cancer

types, and is expected as a treating agent of the cancer type which shows the existing anticancer agent tolerance.
The effect of this invention compound was checked by the following examinations.
Example 1 of an examination Cancer cell growth inhibition examination (test method) Cell culture: HeLaS3 cell or A375 cell is Dalbeco which added FCS 10%. modified eagle It cultivated by medium (DMEM) (GIBCO).
Compound evaluation: In DMEM, seeding of uterine-cervix-carcinoma HeLaS3 cell or the melanoma A375 cell was carried out to the gelatin coat 96 hole plate (made by IWAKI), and it was cultured overnight. The last concentration of DMSO is made the same at 0.1% on the next day, the DMSO solution of an evaluation compound is added by various concentration, and it is Alarmar 48 hours after addition. The color reaction by Blue (Biosource) estimated the proliferation of cells.
(Result) The compound (I) of this invention and (II) checked multiplication of the cancer cell good, and the IC50 value was below 1microM.
Moreover, the compound (I) of this invention and (II(s)) are other cancer cells (non-small cell lung cancer (EKVX, HOP-92, NCI-H358, A-549, NCI-H460)). A breast cancer (MDA-MB-231, MCF7), a prostatic cancer (PC-3), It had good proliferation-of-cells prevention activity similarly to a pancreatic cancer (MIA PaCa-2), colon cancer (WiDr), a renal cancer (A-498), gastric cancer (MKN28), vesical cancer (UC-14), and fibrosarcoma (HT-1080).
Example 2 of an examination in vivo cancer growth inhibition examination (test method) 2x106 of A375 cell strain which is a melanoma were transplanted to the back hypodermic of a male Balb/c nude mouse. The evaluation compound was administered intravenously once per two-week day from the time of tumor capacity reaching [three] in 50-100mm. Moreover, the physiological saline was administered intravenously to the control group. For measurement of the diameter of a tumor, it measured temporally till the next day of the last administration using slide calipers. Tumor capacity was computed in the following formulas.
Tumor capacity (mm3) = 1 / 2x [minor axis (mm)] 2x major axis (mm)
(Result) In the exam, this invention compound (I) and (II) controlled cancer multiplication good, for example, the compound of work examples 4, 37, 118, 121, 148, 154, 180, and 182 showed 50% or more of multiplication control activity to the control group in 0.3 or 1mg/kg of administration.
this invention compound showed good cancer multiplication depressant action similarly in the animal model which transplanted other cancer cells (a prostatic cancer (PC-3) or non-small cell lung cancer (NCI-H358, A-549, NCI-H460)).
Example 3 of an examination Single-dose administration of this invention compound was carried out to the mouse single-dose-toxicity-study (test method) Balb/C mouse by intravenous administration, and the existence of the example of death of a during [the observation period for two weeks] was examined.
(Result) In 3mg [/kg] single-dose administration, the example of death all did not have the compound of the work examples 4, 9, 35, 37, 52, 72, 121, 133, 148, 154, 158, 180, 182, 184, 185, 186, 192, and 197 of this invention. On the other hand in 3mg [/kg] single-dose administration, as for the earlier literature Khim, Pharm.Zh., 32 (6), KP-1 that were indicated by 10-11 (1998), and KP-3, the example of all [in two examples] died, respectively. Therefore, it was shown that this invention compound has low toxicity as compared with an earlier literature compound.
Therefore, it was shown that it is useful as a treating agent of cancer which this invention compound (I) and (II) have good antitumor activity to two or more cancer types, and has a good profile from moreover it being low toxicity.
The medicine constituent of this invention can be prepared by one sort of the compound shown by a general formula (I) or (II) or two sorts or more, and the method usually used using the carriers (the carrier for drugs, an excipient, etc.) which are usually used in the field for the time being, and which are permitted pharmaceutically. Administration may be which form of the parenteral administration by injections, such as internal use by a tablet, a pill, a capsule, the granule, powder, liquid

medicine, inhalations, etc. or intravenous injection, and intramuscular injection, suppositories, ophthalmic solutions, an ophthalmic ointment, the liquid medicine for transderma, an ointment, the patches for transderma, permucosal liquid medicine, permucosal patches, etc.

A tablet, powder, a granule, etc. are used as a solid constituent for internal use by this invention. Set to such a solid constituent. **, one, or the active substance beyond it is mixed with at least one inactivity excipient, for example, milk sugar, a mannitol, grape sugar, hydroxypropylcellulose, a microcrystal cellulose, a starch, a polyvinylpyrrolidone, magnesium aluminometasilicate, etc. The constituent may contain disintegrator, such as lubricant, such as an inactivity additive agent, for example, magnesium stearate etc., and carboxy-methyl-starch sodium, and a solubilizing agent according to a conventional method. You may carry out the film of a tablet or the pill by sugar-coating, stomach solubility, or an enteric coating agent as occasion demands.

The liquid constituent for internal use contains the inactivity solvent generally used, for example, purified water, and ethanol including an emulsion, liquid medicine, suspension, syrups, elixirs, etc. which are permitted in drugs. This constituent may contain a solubilizer, a wetting agent, an auxiliary material like a suspending agent, a sweetening agent, corrigent, the aromatic, and the preservative in addition to an inactivity solvent.

As injections for parenteral administration, sterile water or non-aqueous liquid medicine, suspension, and an emulsion are contained. As a water solvent, distilled water for injection and a physiological saline are contained, for example. As a non-aqueous solvent, there are propylene glycol, a polyethylene glycol, vegetable oil like olive oil, alcohols like ethanol, polysorbate 80 (brand name), etc., for example. Such a constituent may also contain an isotonizing agent, a preservative, a wetting agent, an emulsifier, a dispersing agent, a stabilizing agent, and a solubilizing agent further. These are sanitized by the combination or radiation of filtration and a fungicide which lets for example, a bacteria suspension filter pass. Moreover, these manufacture a sterile solid constituent, and they can also use it for non-bacterial water or the sterile solvent for injection before use, dissolving and suspending it in it.

Usually, when 50mg/kg of doses on the 1st are preferably administered intravenously in 0.01-30mg/kg from about 0.001 in internal use, it is suitable [10mg/kg kg] for the dose on the 1st in 3mg /respectively from about 0.001 preferably from about 0.0001, and it is this. A medicine is prescribed for the patient in 1 time per or two or more steps day. A dose is suitably determined according to each case in consideration of condition, age, sex, etc.

The best form for inventing Based on a work example, this invention is explained still in detail hereafter. this invention compound is not limited to a compound given in the following work example at all. In addition, the example of manufacture of the raw material compound of this invention compound is shown in the example of reference.

Example 1 of reference: Saturated ammonia water (17ml) and Raney nickel (3.0g) were added to the ethanol (50ml) solution of the 3-cyano 2-(dimethylamino) pyridine (2.45g), and it agitated at the room temperature under the hydrogen atmosphere of breath pressure for 8 hours. The catalyst was ****(ed) after 760ml of hydrogen absorption. Mother liquor was condensed and the yellow oil-like 3-(aminomethyl)-2-(dimethylamino) pyridine (2.61g) was obtained.

Example 2 of reference: Several drops of strong sulfuric acid was added to the acetic anhydride (100ml) solution of 2-chloro 3-[(2-methoxy ethyl) amino]-1 and 4-naphtoquinone (33g), and it agitated at 45 degrees C for 1 hour. Ethanol (100ml) was added to reaction mixture, and the superfluous acetic anhydride was esterificated. Ethyl acetate was added after radiationnal cooling and it dried with anhydrous sodium sulfate after washing with water and saturation saline solution. The solvent was distilled off, the residue was crystallized from diethylether and N-(3-chloro 1, 4-dihydro1, 4-dioxo 2-naphtha RENIRU)-N-(2-methoxy ethyl) acetamido (29g) of yellow powder was obtained.

Example 3 of reference: 2-methoxy ethylamine (0.8ml) was added to the benzene (20ml) solution of N-(3-chloro 1, 4-dihydro1, 4-dioxo 2-naphtha RENIRU) acetamido (1.0g), and it agitated under the room temperature for 1 hour. Water was

added to reaction mixture and chloroform extracted. The organic layer was dried with anhydrous sodium sulfate after washing with water and saturation saline solution. The solvent was distilled off, recrystallization of the residue was carried out from ethyl acetate, and N-[3-(2-methoxy ethyl) amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU] acetamido (0.87g) of red powder was obtained.

Example 4 of reference: 2-(aminomethyl) pyrazine (3.2g) and diisopropyl ethylamine (5.8ml) were added to the benzene (90ml) solution of 2, 3-dichloro 1, 4-dihydro1, and 4-dioxo naphthalene (3.0g), and it agitated under the room temperature for 8 hours. The solid which added water to reaction mixture and deposited was ****(ed), and ethyl acetate extracted filtrate. The organic layer was dried with anhydrous sodium sulfate after washing with water and saturation saline solution. Silica gel column chromatography (eluted under chloroform) refined the residue after distilling off a solvent, and 2-chloro [of brown powder] 1, 4-dihydro1, and 4-dioxo 3-[(2-pyrazinyl methyl) amino] naphthalene (0.23g) was obtained.

Example 5 of reference: Chlorination 2-chloro acetyl (3.3ml) was added to 1 of 2-chloro 1, 4-dihydro3-methylamino 1, and 4-dioxo naphthalene (2.2g), and 4-dioxane (30ml) solution, and it agitated under flowing back for 14 hours. The solvent was distilled off after cooling reaction mixture radiationally. The solid which added ethanol to the residue and deposited was ****(ed). The obtained solid was recrystallized from ethanol and 2-chloro N-(3-chloro 1, 4-dihydro1, 4-dioxo 2-naphtha RENIRU)-N-methyl acetamido (2.6g) of yellow powder was obtained.

Example 6 of reference: NaH (440mg) was added to the DMF (20ml) solution of the 2-oxo-piperidine (1.0g), and it agitated for 30 minutes at the room temperature. This solution was added to the DMF (150ml) solution of 2, 3-dichloro 1, 4-dihydro1, and 4-dioxo naphthalene (6.9g) at a stretch, and it agitated at the room temperature for 17 hours. Reaction mixture was opened in saturated ammonia water, the depositing solid was ****(ed), and ethyl acetate extracted filtrate. The organic layer was dried with anhydrous sodium sulfate after washing with water and saturation saline solution. Silica gel column chromatography (eluted with ethyl acetate hexane 1:10 solution) refined the residue after distilling off a solvent, and 2-chloro [of brown powder] 1, 4-dihydro1, and 4-dioxo 3-(2-oxo-piperidino) naphthalene (0.49g) was obtained.

Example 7 of reference: 2-methoxy ethylamine (1.6ml) was added to the tetrahydrofuran (100ml) solution of 4, 7-dihydro4, and 7-dioxo [benzob] thiophene 2-carboxylic acid methyl (2.4g), and it agitated at the room temperature for 27 hours. Silica gel column chromatography (eluted under chloroform) refined the residue after distilling off a solvent, and 4 of yellow powder, the 7-dihydro5-(2-methoxy ethyl) amino 4, and 7-dioxo [benzob] thiophene 2-carboxylic acid methyl (1.5g) were obtained.

Example 8 of reference: Five drops of strong sulfuric acid was added to the acetic anhydride (20ml) solution of 4, the 7-dihydro5-(2-methoxy ethyl) amino 4, and 7-dioxo [benzob] thiophene 2-carboxylic acid methyl (1.2g), and it agitated at the room temperature for 1 hour. The solvent was distilled off after adding methanol (20ml) to reaction mixture gradually. Water was added to the residue and ethyl acetate extracted. The organic layer was dried with anhydrous sodium sulfate after washing with water and saturation saline solution. Solvent Silica gel column chromatography (eluted with ethyl acetate hexane 1:1 solution) refines a residue after distilling off. Dark reddish-brown oil-like 5-[N-acetyl N-(2-methoxy ethyl) amino]-4, 7-dihydro4, and 7-dioxo [benzob] thiophene 2-carboxylic acid methyl (0.39g) was obtained.

The compound of the example 16 of reference which shows the compound of the examples 13-15 of reference which show the compound of the example 12 of reference which shows the compound of the examples 9-11 of reference shown in Table 3 in Table 4 like the example 2 of reference like the example 1 of reference in Table 4 like the example 3 of reference in Table 4 like the example 5 of reference was obtained, respectively.

Work example 1: 2M sodium hydroxide aqueous solution (0.9ml) was added to the ethanol (10ml) solution of N-[3-(2-methoxy ethyl) amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU] acetamido (0.5g), and it agitated for 15 minutes

under the room temperature. Water was added to reaction mixture and ethyl acetate extracted. The organic layer was dried with anhydrous sodium sulfate after washing with water and saturation saline solution. The solvent was distilled off, the residue was washed in **** and ethanol, and 1-(2-methoxy ethyl)-2-methyl [of light orange powder] 4, 9-dihydro4, and 9-dioxo 1H-[2 and 3-naphth d] imidazole (0.58g) was obtained.

Work example 2: Benzylamine (0.5ml) was added to the benzene (15ml) solution of N-(3-chloro 1, 4-dihydro1, 4-dioxo 2-naphtha RENIRU)-N-(2-methoxy ethyl) acetamido (0.5g), and it agitated at the room temperature for 4 hours. Ethyl acetate was added to reaction mixture and it dried with sulphuric anhydride magnesium after washing with water and saturation saline solution. The solvent was distilled off, the residue was crystallized from ethyl acetate hexane, and N-(3-benzylamino 1, 4-dihydro1, 4-dioxo 2-naphtha RENIRU)-N-(2-methoxy ethyl) acetamido (0.51g) of red powder was obtained.

Work example 3: It is 80%3-chloro perbenzoic acid (0.6g) to the dichloromethane (20ml) solution of N-(2-methoxy ethyl)-N-[3-(3-pyridyl methyl) amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU] acetamido (0.95g). In addition, it agitated at the room temperature for 18 hours. The saturation sodium bicarbonate aqueous solution was added to reaction mixture, and it extracted in dichloromethane. The organic layer was dried with anhydrous sodium sulfate after washing with water and saturation saline solution. Solvent Distill off and silica gel column chromatography (eluted with 10:1:0.chloroform methanol saturated ammonia water 1 solution) refines a residue. The 3-[({3-[N-acetyl N-(2-methoxy ethyl)] amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU} amino) methyl] pyridine 1-oxide (0.84g) of the brown amorphous-like solid was obtained.

Work example 4: [the ethanol (30ml) solution of chlorination 1-(2-methoxy ethyl)-2-methyl 3-(4-pyridyl methyl)-4, 9-dihydro4, and 9-dioxo 1H-[2 and 3-naphth d] imidazole 3-IUMU a little salt acid chloride (1.1g)] 1M sodium hydroxide aqueous solution (5.0ml) In addition, it agitated for 30 minutes at the room temperature. Water was added to reaction mixture and ethyl acetate extracted. The organic layer was dried with sulphuric anhydride magnesium after washing with water and saturation saline solution. The solvent was distilled off and silica gel column chromatography (fraction A: eluted in elution and fraction B:ethyl acetate with ethyl acetate hexane 1:1 solution) refined the residue. Fraction A was crystallized from diethylether and N-[3-(2-methoxy ethyl) amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU]-N-(4-pyridyl methyl) acetamido (0.2g) of red powder was obtained. In addition, it is although Fraction B was crystallized from ethyl acetate and yellow powder (0.31g) was obtained, This was the same compound as N-(2-methoxy ethyl)-N-[3-(4-pyridyl methyl) amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU] acetamido of after-mentioned work-example 37 description.

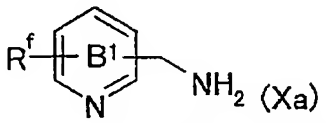
Work example 5: It is 80%3-chloro perbenzoic acid (0.78g) to the dichloromethane (10ml) solution of N-methyl N-{3-[2-(methyl sulfinyl) ethyl] amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU} acetamido (0.52g). In addition, it agitated at the room temperature for 3 hours. The saturation sodium bicarbonate aqueous solution was added to reaction mixture, and it extracted in dichloromethane. The organic layer was dried with anhydrous sodium sulfate after washing with water and saturation saline solution. Solvent Distill off and silica gel column chromatography (eluted with chloroform methanol 50:1 solution) refines a residue. N-methyl N-{3-[2-(methylsulfonyl) ethyl] amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU} acetamido (0.39g) of the orange amorphous-like solid was obtained.

Work example 6: N-[3-(2-hydroxyethyl) amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU]-N-methyl acetamido (0.4g) After carrying out a suspension to ethanol (3ml), 4M hydrogen chloride / ethyl acetate solution (3ml) was added, and it agitated at 45 degrees C for 1 hour. **** and ethyl acetate washed the produced precipitation after radiationnal cooling. The obtained solid was recrystallized from ethanol ethyl acetate, and chlorination 1-(2-hydroxyethyl)-2 in end of non-color powder, 3-dimethyl 4, 9-dihydro4, and 9-dioxo 1H-[2 and 3-naphth d] imidazole 3-IUMU (0.28g) was obtained.

Work example 7: The benzyl bromide (1.9ml) was added to the acetonitrile (20ml) solution of 1-isopropyl 2-methyl 4, 9-dihydro4, and 9-dioxo 1H-[2 and 3-naphth d] imidazole (0.8g), and it agitated under flowing back for 6 hours. **** and ethyl acetate washed the produced precipitation after radiationnal cooling. The obtained solid was recrystallized from methanol and bromination 1-benzyl 3-isopropyl 2-methyl [of yellow powder] 4, 9-dihydro4, and 9-dioxo 1H-[2 and 3-naphth d] imidazole 3-IUMU (0.47g) was obtained.
work example 8: the same method as a work example 6 -- N-(2-methoxy ethyl)- [acetamido / (0.49g) / N-{3-[(2-methoxy 3-pyridyl) methyl] amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU}] The chlorination 1-(2-hydroxy 3-pyridyl) methyl 3-(2-methoxy ethyl)-2-methyl 4 of brown powder, 9-dihydro4, and 9-dioxo 1H-[2 and 3-naphth d] imidazole 3-IUMU (0.39g) It obtained.
Work example 9: They are 4M hydrogen chloride / ethyl acetate solution (10ml) to the ethanol (10ml) solution of N-{3-[(6-chloro 3-pyridyl) methyl] amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU}-N-(2-methoxy ethyl) acetamido (0.8g). In addition, it agitated for one day at the room temperature. Solvent **** and ethyl acetate wash a residue after distilling off. The chlorination 1-[(6-chloro 3-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4 of thin yellow powder, 9-dioxo 4, and 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU (0.82g) were obtained.
work example 10: They are 2M dimethyl amine / tetrahydrofuran solution (3.0ml) to the tetrahydrofuran (30ml) solution of 2-chloro N-[1, 4-dihydro3-(2-methoxy ethyl) amino 1, and 4-dioxo 2-naphtha RENIRU]-N-methyl acetamido (0.5g). In addition, it agitated at the room temperature for 18 hours. Water was added to reaction mixture and ethyl acetate extracted. The organic layer was dried with sulphuric anhydride magnesium after washing with water and saturation saline solution. The residue was crystallized from ethanol after distilling off a solvent, and N-[1, 4-dihydro3-(2-methoxy ethyl) amino 1, and 4-dioxo 2-naphtha RENIRU]-N-methyl 2-(dimethylamino) acetamido (0.19g) of brown powder was obtained.
Work example 11: It is 2-methoxy ethylamine (0.15ml) to the tetrahydrofuran (30ml) solution of 5-[N-acetyl N-(2-methoxy ethyl) amino]-4, 7-dihydro4, and 7-dioxo [benzob] thiophene 2-carboxylic acid methyl (0.39g). In addition, it agitated at the room temperature for 6.5 hours. Solvent Silica gel column chromatography (eluted with hexane ethyl acetate 50:1 solution) refines a residue after distilling off. Purplish red color oil-like 4 [5-[N-acetyl N-(2-methoxy ethyl) amino]-], the 7-dihydro6-(2-methoxy ethyl) amino 4, and 7-dioxo [benzob] thiophene 2-carboxylic acid methyl (0.39g) were obtained.
Work example 12: They are 4M hydrogen chloride / ethyl acetate solution (2.5ml) to the methanol (30ml) suspension of 3-{[4[the 3-(N-acetyl N-methyl) amino 1, 4-dihydro1, and]-dioxo 2-naphtha RENIRU] Amino} pro PIONAMIDO (0.32g). In addition, it agitated at the room temperature for 16 hours. The solvent was distilled off after radiationnal cooling and heating churning of the residue was carried out in ethanol. The produced precipitation was washed by **** and ethanol after radiationnal cooling, and chlorination 1-(2-carboxyethyl)-4 in end of non-color powder, 9-dihydro2, 3-dimethyl 4, and 9-dioxo 1H-[2 and 3-naphth d] imidazole 3-IUMU (0.15g) was obtained.
The work-example compound of the description was obtained to the after-mentioned tables 6-20 like the above-mentioned work examples 1-9.
The constitutional formula and physicochemical character of a work-example compound are shown in the after-mentioned tables 3-5 in Tables 6-20 at the row of the example compound of reference, respectively. Moreover, almost like a method given in said work example or a manufacturing method, the compound [thing mentioned above / Tables 21-27 / a compound / a chemical structure type] applies some obvious strange method to a person skilled in the art at them, or is manufactured easily.
The cable address in front is an example Sy:manufacturing method of Ref:reference ([a number / the number of said work

example / show and]).; Ex: Work example; Co: Compound number; Sal: Salt; It is the same method as said this work example about the compound concerned. [having manufactured] it is shown -- Dat:physicochemical character; Do not do -:existence of.; (F:FAB-MS(M)+; F+:FAB-MS(M)-; F+:FAB-MS(M+H)+; F-:FAB-MS(M-H)-; E:EI-MS(M)+;) characteristic peak deltappm of N1:1 H-NMR (DMSO-d6, TMS internal standard); i-Pr: -- isopropyl; c-Pr:cyclo propyl; Ad:1-adamanthyl; Ac: -- acetyl; Bn: -- benzyl; Pipe; -- piperidino; Morp; -- morpholino; Py2;2-pyridyl; Py3;3-pyridyl; Py4;4-pyridyl; Th;2-thienyl; Fu;2-furil; Thf;2-tetrahydrofuranyl; Pyr;2-pyrazinyl; 5-MePyr;5-methyl pyrazine 2-IRU; Pym;4-pyrimidinyl; Qu;3-quinolyl; Dio;4-benzodioxolyl; Im;4-imidazolyl; Bim;2-benzoimidazolyl; -- and -- In;2-India Lil is shown, respectively. In addition, it is shown that the number in front of a substituent shows a substitution position, for example, -Cl replaces it by 3, 4-Cl:3 place, and the 4th place, respectively.

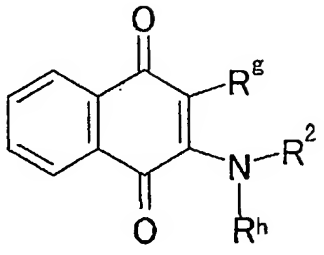
表3



(Xa)

Ref	B^1	$-R^f$	Dat	Ref	B^1	$-R^f$	Dat
1	Py3	2-NMe_2	F+: 152	10	Py4	2-NMe_2	F+: 152
9	Py3	6-NMe_2	F+: 152	11	Py3	2-OMe	E: 138

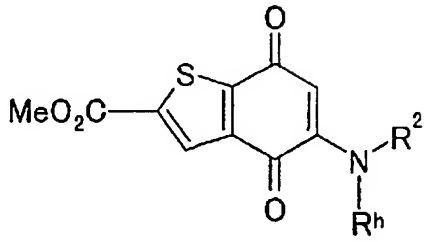
表4



(IVa) or (VIa) or (VIIIa)

Ref	-R^g	-R^h	R^2	Dat
2	-Cl	-Ac	-$(CH_2)_2OMe$	N1: 1.88(3H,s), 2.99(3H,s), 3.3-3.9(4H,m), 7.9-8.2(4H,m)
3	-NH-$(CH_2)_2OMe$	-Ac	-H	F+: 289
4	-Cl	-H	-CH_2Pyr	F': 299
5	-Cl	-$COCH_2Cl$	-Me	F: 298
6	-Cl	-$CO(CH_2)_4$-		F+: 290
12	-Cl	-Ac	-CH_2Pyr	F': 341
13	-NH-CH_2(Py3)	-Ac	-H	F+: 322
14	-NH-CH_2(Py4)	-Ac	-H	F+: 322
15	-NH-CH_2(Pyr)	-Ac	-H	F+: 323
16	-Cl	-$COCH_2OMe$	-Me	F+: 294

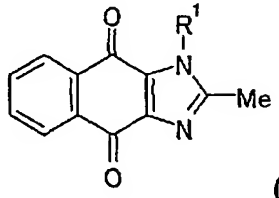
表5



(IVb) or (VIIIb)

Ref	R^h	R^2	Dat
7	-H	$-(CH_2)_2OMe$	F+: 296
8	-Ac	$-(CH_2)_2OMe$	F+: 338

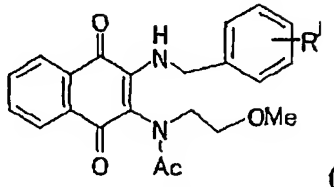
表6



(IIIa)

Ex.	$-R^1$	Dat	Ex.	$-R^1$	Dat
1	$-(CH_2)_2OMe$	F+: 271	14	$-CH_2$(Py4)	F+: 304
13	$-CH_2$(Py3)	F+: 304	15	$-CH_2$(Pyr)	F+: 305

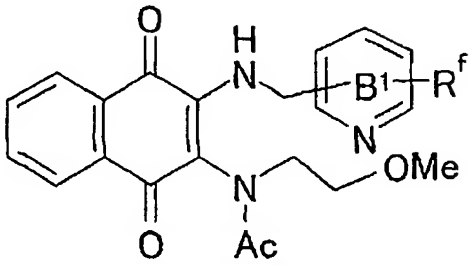
表7



(IIc)

Ex	-R^1	Sy	Dat
2	-H	-	F+: 379 N1: 1.34(3H,br), 3.06(3H,s), 3.1-3.8(4H,m), 4.5-4.8(2H,m), 7.2-7.4(5H,m), 7.77(1H,dt), 7.85(1H,dt), 7.93(1H,br), 7.98(1H,d), 8.03(1H,d)
16	2-Cl	2	F+: 413
17	3-Cl	2	F+: 413
18	4-Cl	2	F+: 413 N1: 1.39(3H,br), 3.06(3H,s), 3.1-3.4(2H,m), 3.4-3.5(1H,m), 3.6-3.9(1H,m), 4.5-4.8(2H,m), 7.27(2H,d), 7.38(2H,d), 7.7-8.1(4H,m)
19	3,4-Cl	2	F: 447
20	2-OMe	2	F+: 409
21	3-OMe	2	F+: 409
22	4-OMe	2	F+: 409
23	4-Ph	2	F+: 455
24	2-CN	2	F+: 404
25	3-CN	2	F+: 404
26	4-CN	2	F+: 404
27	4-SO_2NH_2	2	F+: 458
28	4-CF_3	2	F+: 447
29	4-F	2	F+: 397 N1: 1.40(3H,br), 3.06(3H,s), 3.1-3.6(3H,m), 3.79(1H,br), 4.5-4.8(2H,m), 7.1-7.2(2H,m), 7.2-7.5(2H,m), 7.7-8.2(4H,m)
30	4-Br	2	F+: 457, 459
31	3-CH_2NH_2	2	F+: 408
32	4-CH_2NH_2	2	F: 407
33	3-NO_2	2	F+: 424
34	4-NO_2	2	F+: 424 N1: 1.39(3H,br), 3.07(3H,s), 3.1-3.6(3H,m), 3.6-3.9(1H,m), 4.6-5.0(2H,m), 7.54(2H,d), 7.7-8.2(5H,m), 8.19(2H,d)

表8

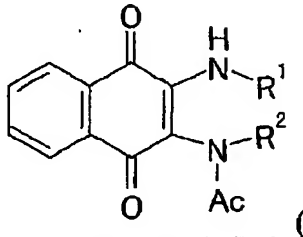


(IId)

Ex	B^1	$-R^f$	Sy	Dat
3	Py3	1-oxide	-	F+: 396
35	Py3	-H	2	F+: 380 N1: 1.40(3H,s), 3.06(3H,s), 3.1-3.8(4H,m), 4.6-4.8(2H,m), 7.34(1H,dd), 7.6-8.1(6H,m), 8.4-8.5(2H,m)
36	Py2	-H	2	F+: 380 N1: 1.62(3H,s), 3.06(3H,s), 3.2-3.9(4H,m), 4.5-5.0(4H,m), 7.2-7.5(2H,m), 7.7-8.2(6H,m), 8.54(1H,d)
37	Py4	-H	2	F+: 380 N1: 1.38(1H,br), 3.07(3H,s), 3.1-3.8(4H,m), 4.6-4.8(2H,m), 7.26(2H,d), 7.77(1H,dt), 7.85(1H,dt), 7.95(1H,d), 8.01(1H,d), 8.48(2H,d)
38	Py3	2-Cl	2	F+: 414 N1: 1.49(3H,s), 3.07(3H,s), 3.1-3.4(2H,m), 3.4-3.6(1H,m), 3.6-3.8(1H,m), 4.6-4.9(2H,m), 7.3-7.5(1H,m), 7.7-8.2(6H,m)
39	Py3	6-Cl	2	F+: 414 N1: 1.47(3H,br), 3.07(3H,s), 3.1-3.6(3H,m), 3.6-4.0(1H,m), 4.6-4.9(2H,m), 7.48(1H,d), 7.6-8.1(6H,m), 8.34(1H,d)
40	Py3	2-OMe	2	F+: 410
41	Py3	6-OMe	2	F+: 410 N1: 1.49(3H,s), 3.07(3H,s), 3.1-3.5(3H,m), 3.6-3.9(4H,m), 4.5-4.8(2H,m), 6.79(1H,d), 7.5-7.7(1H,m), 7.7-8.2(5H,m)
42	Py3	2-NMe$_2$	2	F+: 423

42	Py3	2-NMe_2	2	F+: 423
43	Py3	6-NMe_2	2	F+: 423
44	Py3	5-Me	2	F+: 394
45	Py3	6-Me	2	F: 393
46	Py3	6-CF_3	2	F+: 448
47	Py4	2-Cl	2	F+: 414 N1: 1.48(3H,br), 3.09(3H,s), 3.1-3.6(3H,m), 3.6-3.9 (1H,m), 4.5-5.0(2H,m), 7.33(1H,d), 7.45(1H,s), 7. 6-8.2(5H,m), 8.34(1H,d)
48	Py4	2-NMe_2	2	F+: 423
49	Py4	2-OMe	2	F+: 410

表 9

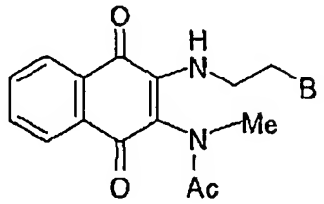


(IIe)

Ex	-R^1	-R^2	Sy	Dat
4	-$(CH_2)_2OMe$	-CH_2(Py4)	-	F+: 380 N1: 1.19(3H,s), 3.26(3H,s), 3.47(4H,br), 4.27 (1H,d), 4.81(1H,d), 7.10(1H,br), 7.35(2H,d), 7.74(1H,dt), 7.82(1H,dt), 7.92(1H,d), 7.98(1H,d), 8.41(2H,d)
50	-$(CH_2)_2OMe$	-$(CH_2)_2OMe$	2	N1: 1.83(3H,s), 3.0-3.8(14H,m), 6.9-7.1(1H,m), 7.7-7.9(2H,m), 7.9-8.1(2H,m)
51	-$(CH_2)_2OMe$	-Bn	2	N1: 1.88(3H,s), 3.23(3H,s), 3.3-3.5(4H,m), 4. 4-4.7(2H,m), 6.91(1H,br), 7.1-7.4(5H,m), 7.6 -8.1(4H,m)
52	-$(CH_2)_2OMe$	-CH_2(Py3)	4	F+: 380 N1: 1.87(3H,s), 3.25(3H,s), 3.4-3.6(4H,m), 4. 31(1H,d), 4.81(1H,d), 7.08(1H,br), 7.23(1H, dd), 7.6-7.8(2H,m), 7.81(1H,t), 7.88(1H,d), 7.98(1H,d), 8.37(1H,d), 8.45(1H,s)
53	-Bn	-Bn	2	F+: 411
54	-CH_2(Py4)	-Bn	2	F+: 412

54	-CH_2(Py4)	-Bn	2	F+: 412
55	-CH_2(Py3)	-Bn	2	F+: 412
56	-$(CH_2)_2$Ph	-$(CH_2)_2$OMe	2	F+: 393
57	-CH_2Th	-$(CH_2)_2$OMe	2	F+: 387
58	-CH_2Fu	-$(CH_2)_2$OMe	2	F+: 369
59	-CH_2Pyr	-$(CH_2)_2$OMe	2	F+: 381 N1: 1.60(3H,s), 3.07(3H,s), 3.2-3.8(4H,m), 4.5-5.3(2H,m), 7.5-8.2(5H,m), 8.5-8.8(3H,m)
60	-CH_2Qu	-$(CH_2)_2$OMe	2	F+: 430
61	-$(CH_2)_2$(Py2)	-$(CH_2)_2$OMe	2	F+: 394
62	-$(CH_2)_2$(Py3)	-$(CH_2)_2$OMe	2	E: 393
63	-$(CH_2)_2$(Py4)	-$(CH_2)_2$OMe	2	F+: 394
64	-$(CH_2)_2$In	-$(CH_2)_2$OMe	2	F+: 432
65	-CH_2Dio	-$(CH_2)_2$OMe	2	F+: 423
66	-$(CH_2)_3$Im	-$(CH_2)_2$OMe	2	F+: 397
67	-$(CH_2)_2$Im	-$(CH_2)_2$OMe	2	F+: 383
68	-CH_2Bim	-$(CH_2)_2$OMe	2	F+: 419
69	-$(CH_2)_2O(CH_2)_2NH_2$	-$(CH_2)_2$OMe	2	F+: 376
70	-$(CH_2)_5NH_2$	-$(CH_2)_2$OMe	2	F+: 374
71	-$(CH_2)_2O(CH_2)_2$-$O(CH_2)_2NH_2$	-$(CH_2)_2$OMe	2	F+: 420

表１０

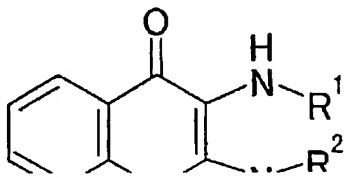


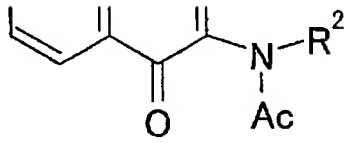
(IIf)

Ex	-B	Sy	Dat
5	-SO_2Me	-	F+: 351
72	-OMe	2	F+: 303 N1: 1.83(3H,s), 2.92(3H,s), 3.29(3H,s), 3.4-3.7(4H,m), 7.11(1H,br), 7.7-7.9(2H,m), 7.9-8.1(2H,m)
73	-OPh	2	N1: 1.83(3H,s), 2.93(3H,s), 3.6-3.9(2H,m), 4.21(2H,t), 6.8-7.1(3H,m), 7.2-7.5(3H,m), 7.7-7.9(2H,m), 7.9-8.1(2H,m)
74	-OBn	2	N1: 2.89(3H,s), 3.90(2H,t), 4.19(3H,s), 4.45(2H,s), 4.89(2H,s), 7.1-7.5(5H,m), 7.9-8.1(2H,m), 8.1-8.2(2H,m)

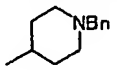
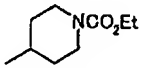
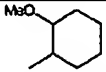
74	-OBn	2	N1: 2.69(3H,s), 3.90(2H,t), 4.19(3H,s), 4.45(2H,s), 4.69(2H,t), 7.1-7.5(5H,m), 7.9-8.1(2H,m), 8.1-8.3(2H,m)
75	-NMe_2	2	F+: 316 N1: 1.83(3H,s), 2.18(6H,s), 2.4-2.6(2H,m), 2.94(3H,s), 3.2-3.5(2H,m), 7.14(1H,t), 7.7-7.9(2H,m), 7.9-8.1(2H,m)
76	-OEt	2	F+: 317 N1: 1.10(3H,t), 1.82(3H,s), 2.92(3H,s), 3.3-3.7(6H,m), 7.09(1H,br), 7.7-7.9(2H,m), 7.9-8.1(2H,m)
77	-OPr	2	F+: 331 N1: 0.85(3H,t), 1.4-1.6(2H,m), 1.83(3H,s), 2.92(3H,s), 3.37(2H,t), 3.4-3.7(4H,m), 7.08(1H,br), 7.7-7.9(2H,m), 7.9-8.1(2H,m)
78	-O(i-Pr)	2	F+: 331 N1: 1.07(6H,d), 1.82(3H,s), 2.92(3H,s), 3.4-3.7(5H,m), 7.08(1H,br), 7.7-7.9(2H,m), 7.9-8.1(2H,m)
79	-$O(CH_2)_2NH_2$	2	F+: 332
80	-OCH_2(Py3)	2	F+: 413 N1: 1.79(3H,s), 2.90(3H,s), 3.5-3.8(4H,m), 4.55(2H,s), 7.1-7.3(1H,m), 7.2-7.5(1H,m), 7.7-7.9(3H,m), 7.9-8.1(2H,m), 8.4-8.6(2H,m)
81	-SMe	2	F+: 319
82	-NEt_2	2	F+: 344
83	-N(i-Pr)$_2$	2	F+: 372
84	-Pipe	2	F+: 356
85	-Morp	2	F+: 358
86	-NHAc	2	F+: 330 N1: 1.81(6H,s), 2.90(3H,s), 3.2-3.7(4H,m), 7.36(1H,br), 7.7-8.2(5H,m)
87	-OCONHPh	2	F+: 408
88	-$CONH_2$	2	F+: 316
89	-CN	2	F+: 298
90	-$O(CH_2)_2OMe$	2	F+: 347

表１１





(IIe)

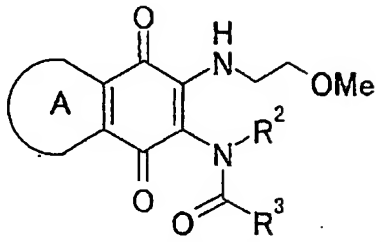
Ex	-R^1	-R^2	Sy	Dat
91	-$(CH_2)_3OMe$	-Me	2	N1: 1.7-2.0(5H,m), 2.92(3H,s), 3.25 (3H,s), 3.3-3.6(4H,m), 7.2-7.5(1H, m), 7.6-8.2(4H,m)
92	-$(CH_2)_3NMe_2$	-Me	2	F+: 330
93	-CH_2(Py2)	-Me	2	F+: 336 N1: 1.5-2.2(3H,m), 2.7-3.0(3H,m), 4.5-5.0(2H,m), 7.2-7.5(2H,m), 7.6-8.3(6H,m), 8.4-8.7(1H,m)
94	-CH_2(Py3)	-Me	2	F+: 336
95	-CH_2(Py4)	-Me	2	F+: 336
96	-CH_2CF_3	-Me	2	F+: 327
97	-CH_2Thf	-Me	2	F+: 329
98	- CH_2CONH_2	-Me	2	F+: 302
99	- CH_2CN	-Me	2	F+: 284
100		-Me	2	F+: 418
101		-Me	2	F': 399
102		-Me	2	F+: 357
103	-CH(Me)Ph	-$(CH_2)_2OMe$	2	F+: 375
104	-CH_2Pym	-$(CH_2)_2OMe$	2	F+: 381 N1: 1.61(3H,s), 3.08(3H,s), 3.2-3.9(4H,m), 4.6-5.0(2H,m), 7.4-7.6(1H, m), 7.7-8.1(5H,m), 8.75(1H,d), 9.12(1H,d)
105	-$(CH_2)_2OMe$	-CH_2Pyr	2	F+: 381 N1: 1.88(3H,s), 3.26(3H,s), 3.4-3.9(4H,m), 4.3-5.3(2H,m), 7.6-8.1(5H, m), 8.3-8.6(2H,m), 8.79(1H,d)
				F+: 395

106	-CH_2(5-MePyr)	-$(CH_2)_2OMe$	2	F+: 395 N1: 1.61(3H,s), 2.47(3H,s), 3.07(3H,s), 3.2-3.8(4H,m), 4.6-5.0(2H,m), 7.7-8.1(5H,m), 8.4-8.6(2H,m)

表１２

Ex	-R^1	-R^2	Sy	Dat
107	-CH_2Pyr	-CH_2Pyr	2	F+: 415 N1: 1.72(3H,s), 4.3-5.3(4H,m), 7.6-8.1(4H,m), 8.2-8.7(5H,m), 8.69(1H,s), 8.79(1H,s)
108	-CH_2(Py4)	-CH_2Pyr	2	F+: 414 N1: 1.58(3H,br), 4.2-5.1(4H,m), 7.29(2H,d), 7.6-8.1(4H,m), 8.28(1H,s), 8.3-8.7(4H,m), 8.78(1H,d)
109	-$(CH_2)_{17}Me$	-$(CH_2)_2OMe$	2	F+: 541
110	-CH_2Ad	-$(CH_2)_2OMe$	2	F: 437
111	-CH_2CHPh_2	-$(CH_2)_2OMe$	2	F: 469
112	-$(CH_2)_2O(CH_2)_2OMe$	-$(CH_2)_2OMe$	2	F: 391 N1: 1.84(3H,s), 3.0-3.9(18H,m), 6.9-7.2(1H,m), 7.7-7.9(2H,m), 7.9-8.1(2H,m)
113	-$(CH_2)_2O(CH_2)_2O(CH_2)_2OMe$	-$(CH_2)_2OMe$	2	F: 435
114	-$(CH_2)_2O$(4-BnO-Ph)	-$(CH_2)_2OMe$	2	F: 515

表１３



(IIg)

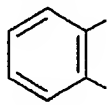
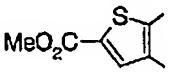
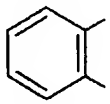
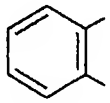
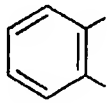
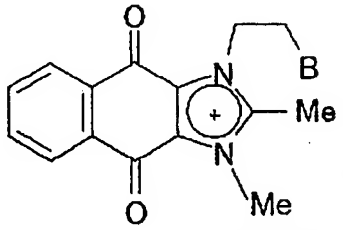
Ex	A	-R^2	-R^3	Sy	Dat
10		-Me	-CH_2NMe_2	-	F+: 346
11		-$(CH_2)_2OMe$	-Me	-	F+: 411
115		-Me	-CH_2Cl	2	F+: 337
116		-Me	-CH_2OMe	2	F+ 333
117		-$(CH_2)_4$-		2	F+: 329

表１４

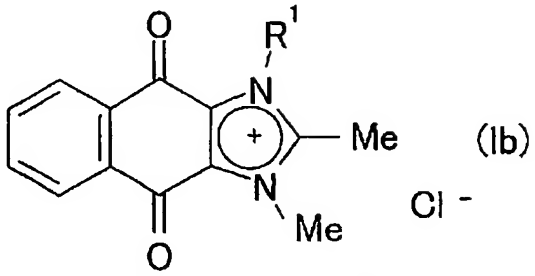


(Ia)

Ex	-B	Sal	Sy	Dat
6	-OH	-	-	F-: 270 N1: 2.90(3H,s), 3.8(2H,br), 4.17(3H,s), 4.74(2H,t), 7.9-8.2(4H,m)

				.2(4H,m)
118	-OMe	-	6	F: 285 N1: 2.89(3H,s), 3.25(3H,s), 3.77(2H,t), 4.20(3H,s), 4.8-5.0(2H,m), 7.9-8.3(4H,m)
119	-OPh	-	6	F-: 346 N1: 3.01(3H,s), 4.21(3H,s), 4.43(2H,t), 5.13(2H,t), 6.8-7.0(3H,m), 7.2-7.4(2H,m), 7.9-8.1(2H,m), 8.1-8.3(2H,m)
120	-OBn	-	6	F-: 360 N1: 2.89(3H,s), 3.90(2H,t), 4.19(3H,s), 4.45(2H,s), 4.89(2H,t), 7.1-7.5(5H,m), 7.9-8.1(2H,m), 8.1-8.3(2H,m)
121	-NMe_2	HCl	6	F: 298 N1: 2.8-3.0(6H,m), 3.02(3H,s), 3.5-3.8(2H,m), 4.16(3H,s), 5.0-5.2(2H,m), 7.9-8.1(2H,m), 8.1-8.3(2H,m), 11.2-11.5(1H,br)
122	-OEt	-	6	F: 299 N1: 1.06(3H,t), 2.89(3H,s), 3.44(2H,q), 3.80(2H,t), 4.20(3H,s), 4.86(2H,t), 7.9-8.1(2H,m), 8.1-8.3(2H,m)
123	-OPr	-	6	F: 313 N1: 0.80(3H,t), 1.3-1.6(2H,m), 2.90(3H,s), 3.35(2H,t), 3.80(2H,t), 4.20(3H,s), 4.87(2H,t), 7.9-8.1(2H,m), 8.1-8.3(2H,m)
124	-O(i-Pr)	-	6	F: 313 N1: 1.02(6H,d), 2.89(3H,s), 3.4-3.7(1H,m), 3.79(2H,t), 4.21(3H,s), 4.83(2H,t), 7.9-8.1(2H,m), 8.1-8.3(2H,m)
125	-$O(CH_2)_2NH_2$	HCl	6	F: 314
126	-OCH_2(Py3)	HCl	6	F: 362 N1: 2.90(3H,s), 3.98(2H,t), 4.21(3H,s), 4.68(2H,s), 4.95(2H,t), 7.8-8.1(3H,m), 8.1-8.4(3H,m), 8.6-8.9(2H,m)
127	-SMe	-	6	F: 301
128	-SO_2Me	-	6	F: 333
129	-NEt_2	HCl	6	E: 326
130	-$N(i\text{-}Pr)_2$	HCl	6	E: 354
131	-Pipe	HCl	6	E: 338
132	-Morp	HCl	6	E: 340

表１５

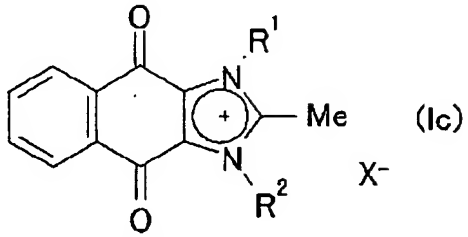


(Ib)

Ex	-R^1	Sal	Sy	Dat
133	-$(CH_2)_2NHAc$	-	6	F: 312 N1: 1.76(3H,s), 2.86(3H,s), 3.4-3.7(2H,m), 4.18(3H,s), 4.69(2H,t), 7.9-8.1(2H,m), 8.1-8.3(2H,m), 8.34(1H,t)
134	-$(CH_2)_2OCONHPh$	-	6	F: 390
135	-$(CH_2)_3OMe$	-	6	F: 299 N1: 2.0-2.2(2H,m), 2.88(3H,s), 3.24(3H,s), 3.42(2H,t), 4.18(3H,s), 4.69(2H,t), 7.9-8.1(2H,m), 8.1-8.3(2H,m)
136	-$(CH_2)_3NMe_2$	HCl	6	F: 312
137	-CH_2(Py2)	HCl	6	F: 318 N1: 2.96(3H,s), 4.25(3H,s), 6.14(2H,s), 7.3-7.6(1H,m), 7.72(1H,d), 7.8-8.3(5H,m), 8.53(1H,d)
138	-CH_2(Py3)	HCl	6	F: 318
139	-CH_2(Py4)	HCl	6	F: 318
140	-CH_2CF_3	-	6	F: 309
141	-$(CH_2)_2CONH_2$	-	6	F: 298
142	-$(CH_2)_2CN$	-	6	F: 280
143	-$(CH_2)_2O(CH_2)_2OMe$	-	6	F: 329
144	-CH_2Thf	-	6	F: 311
145	-CH_2CONH_2	-	6	F: 284
146	-CH_2CN	-	6	F: 266

表１６

表１０

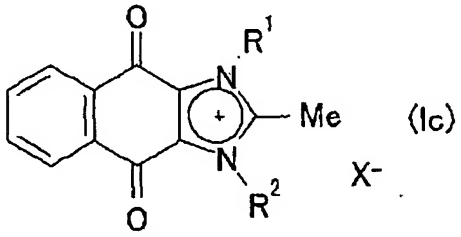


(Ic)

Ex	-R^1	-R^2	X	Sal	Sy	Dat
7	-Bn	-i-Pr	Br	-	-	F: 345 N1: 1.67(6H,d), 2.95(3H,s), 5.44(1H,br), 6.01(2H,s), 7.3-7.5(5H,m), 7.9-8.3(4H,m)
147	-Bn	-$(CH_2)_2$OH	Cl	-	6	F-: 346 N1: 2.88(3H,s), 3.86(2H,t), 4.75(2H,t), 6.02(2H,s), 7.3-7.5(5H,m), 7.9-8.3(4H,m)
148	-$(CH_2)_2$OMe	-$(CH_2)_2$OMe	Cl	-	6	F-: 328 N1: 2.89(3H,s), 3.24(6H,s), 3.78(4H,t), 4.87(4H,t), 7.9-8.1(2H,m), 8.1-8.3(2H,m)
149	-CH_2(Py4)	-Bn	Cl	HCl	6	F: 394
150	-CH_2(Py3)	-Bn	Cl	HCl	6	F: 394
151	-$(CH_2)_2$Ph	-$(CH_2)_2$OMe	Cl	-	6	F: 375
152	-CH_2Th	-$(CH_2)_2$OMe	Cl	-	6	F: 367
153	-CH_2Fu	-$(CH_2)_2$OMe	Cl	-	6	F: 351
154	-CH_2Pyr	-$(CH_2)_2$OMe	Cl	-	6	F: 363 N1: 2.8-3.2(6H,m), 3.84(2H,t), 4.92(2H,t), 6.19(2H,s), 7.8-8.0(2H,m), 8.0-8.2(2H,m), 8.52(1H,dd), 8.62(1H,d), 8.92(1H,d)
155	-CH_2Qu	-$(CH_2)_2$OMe	Cl	HCl	6	F: 412
156	-$(CH_2)_2$(Py2)	-$(CH_2)_2$OMe	Cl	HCl	6	F: 376
157	-$(CH_2)_2$(Py3)	-$(CH_2)_2$OMe	Cl	HCl	6	F: 376
158	-$(CH_2)_2$(Py4)	-$(CH_2)_2$OMe	Cl	HCl	6	F: 376
159	-$(CH_2)_2$In	-$(CH_2)_2$OMe	Cl	-	6	F: 414
160	-CH_2Dio	-$(CH_2)_2$OMe	Cl	-	6	F: 405
161	-$(CH_2)_3$Im	-$(CH_2)_2$OMe	Cl	HCl	6	F: 379 N1: 2.3-2.6(2H,m), 2.98(3H,s), 3.27(3H,s), 3.79(2H,t), 4.45(2H,t), 4.76(2H,t), 4.86(2H,t), 7.73(1H,d), 7.95(1H,d), 7.9-8.1(2H,m), 8.1-8.3(2H,m), 9.40(1H,s), 15.14(1H,br)

						8.1-8.3(2H,m), 9.40(1H,s), 15.14(1H,br)
162	-$(CH_2)_2$Im	-$(CH_2)_2$OMe	Cl	HCl	6	F: 365 N1: 2.71(3H,s), 3.26(3H,s), 3.34(2H,t), 3.79(2H,t), 4.81(2H,t), 5.00(2H,t), 7.50(1H,s), 7.9-8.1(2H,m), 8.1-8.3(2H,m), 9.04(1H,s), 14.76(1H,br), 15.49(1H,br)
163	-CH_2Bim	-$(CH_2)_2$OMe	Cl	HCl	6	F: 401

表１７



Ex	-R^1	-R^2	X	Sal	Sy	Dat
12	-$(CH_2)_2CO_2H$	-Me	Cl	-	-	F+: 299
164	-$(CH_2)_2O(CH_2)_2$-NH_2	-$(CH_2)_2$OMe	Cl	HCl	6	F: 358
165	-$(CH_2)_5NH_2$	-$(CH_2)_2$OMe	Cl	HCl	6	F: 356
166	-$(CH_2)_2O(CH_2)_2$-$O(CH_2)_2NH_2$	-$(CH_2)_2$OMe	Cl	HCl	6	F: 402
167	-CH(Me)Ph	-$(CH_2)_2$OMe	Cl	-	6	F: 375
168	-CH_2(5-MePyr)	-$(CH_2)_2$OMe	Cl	-	6	F: 377 N1: 2.99(3H,s), 3.27(3H,s), 3.82(2H,t), 4.92(2H,t), 6.13(2H,s), 7.9-8.1(2H,m), 8.1-8.3(2H,m), 8.4-8.5(1H,m), 8.7-8.9(1H,m)
169	-CH_2Pyr	-CH_2Pyr	Cl	-	6	F: 397 N1: 3.09(3H,br), 6.24(4H,br), 7.7-8.3(4H,m), 8.5-8.8(4H,m), 9.00(2H,d)
170	-CH_2(Py4)	-CH_2Pyr.	Cl	-	6	F: 396 N1: 2.96(3H,s), 6.11(2H,s), 6.20(2H,s), 7.3-7.5(2H,m), 7.8-8.1(2H,m), 8.0-8.2(2H,m), 8.5-8.8(4H,m), 9.01(1H,d)
171						

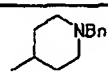
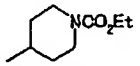
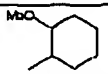
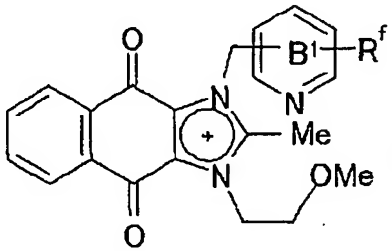
171		-Me	Cl	HCl	6	F: 400
172		-Me	Cl	-	6	F: 382
173		-Me	Cl	-	6	F: 339
174	-$(CH_2)_{17}$Me	-$(CH_2)_2$OMe	Cl	-	6	F: 523
175	-CH_2Ad	-$(CH_2)_2$OMe	Cl	-	6	F: 421
176	-CH_2CHPh_2	-$(CH_2)_2$OMe	Cl	-	6	F: 451
177	-$(CH_2)_2O(CH_2)_2$-OMe	-$(CH_2)_2$OMe	Cl	-	6	F: 373 N1: 2.91(3H,s), 3.15(3H,s), 3.24(3H,s), 3.3-3.4(2H,m), 3.4-3.6(2H,m), 3.79(2H,t), 3.87(2H,t), 4.7-5.0(4H,m), 7.9-8.1(2H,m), 8.1-8.3(2H,m)
178	-$(CH_2)_2O(CH_2)_2$-$O(CH_2)_2$OMe	-$(CH_2)_2$OMe	Cl	-	6	F: 417
179	-$(CH_2)_2O$(4-BnO-Ph)	-$(CH_2)_2$OMe	Cl	-	6	F: 497

表１８

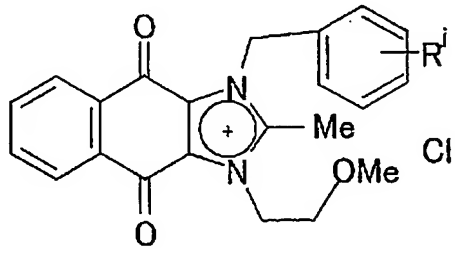


Cl⁻ (Id)

Ex	B^1	-R^f	Sal	Sy	Dat
8	Py3	2-OH	-	-	F: 378
9	Py3	6-Cl	-	-	F: 396 N1: 2.91(3H,s), 3.25(3H,s), 3.79(2H,t), 4.86(2H,t), 6.05(2H,s), 7.59(1H,d), 7.87(1H,dd), 7.9-8.1(2H,m), 8.1-8.3(2H,m), 8.45(1H,d)
180	Py3	H	HCl	6	F: 362 N1: 2.93(3H,s), 3.26(3H,s), 3.80(2H,t), 4.88(2H,t), 6.16(2H,s), 7.8-8.3(6H,m), 8.7-8.9(2H,m)
					F: 362 N1: 2.98(3H,s), 3.28(3H,s), 3.84(2H,t), 4.93(2H,t), 6.17(2

181	Py2	H	HCl	6	N1: 2.98(3H,s), 3.28(3H,s), 3.84(2H,t), 4.93(2H,t), 6.17(2H,s), 7.3-7.6(1H,m), 7.71(1H,d), 7.8-8.4(5H,m), 8.52(1H,d)
182	Py4	H	HCl	6	F: 362 N1: 2.92(3H,s), 3.28(3H,s), 3.83(2H,t), 4.92(2H,t), 6.35(2H,s), 7.9-8.3(6H,m), 8.98(2H,d)
183	Py3	1-oxide	HCl	6	F: 378
184	Py3	2-Cl	HCl	6	F: 396 N1: 2.92(3H,s), 3.28(3H,s), 3.84(2H,t), 4.93(2H,t), 6.03(2H,s), 7.3-7.6(2H,m), 7.9-8.0(2H,m), 8.0-8.3(2H,m), 8.42(1H,dd)
185	Py4	2-OH	-	8	F: 378 N1: 2.84(3H,s), 3.26(3H,s), 3.81(2H,t), 4.88(2H,t), 5.84(2H,s), 5.96(1H,s) ,6.22(1H,dd), 7.44(1H,d), 7.9-8.1(2H,m), 8.1-8.3(2H,m)
186	Py3	6-OMe	HCl	6	F: 392 N1: 2.92(3H,s), 3.24(3H,s), 3.7-4.0(5H,m), 4.6-5.5(2H,m), 5.97(2H,s), 6.87(1H,d), 7.75(1H,d), 7.9-8.1(2H,m), 8.1-8.4(3H,m)
187	Py3	2-NMe_2	HCl	6	F: 405
188	Py3	6-NMe_2	HCl	6	F: 405
189	Py3	5-Me	HCl	6	F: 376
190	Py3	6-Me	HCl	6	F: 376
191	Py3	6-CF_3	HCl	6	F: 430
192	Py4	2-Cl	HCl	6	F: 396 N1: 2.87(3H,s), 3.27(3H,s), 3.81(2H,t), 4.90(2H,t), 6.09(2H,s), 7.3-7.5(3H,m), 7.8-8.4(4H,m), 8.45(1H,d)
193	Py4	2-NMe_2	HCl	6	F: 405

表１９

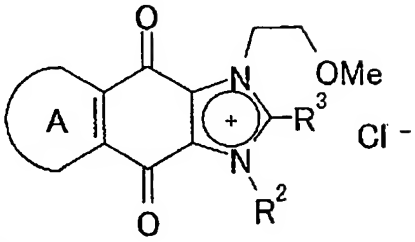


Cl^- (Ie)

Ex	$-R^i$	Sal	Sv	Dat

Ex	-R[i]	Sal	Sy	Dat
194	H	-	6	F: 361 N1:2.85(3H,s), 3.24(3H,s), 3.80(2H,t), 4.88(2H,t), 6.05(3H,s), 7.2-7.5(5H,m), 7.9-8.3(4H,m)
195	2-Cl	-	6	F: 395
196	3-Cl	-	6	F: 395
197	4-Cl	-	6	F: 395 N1: 2.85(3H,s), 3.24(3H,s), 3.79(2H,t), 4.86(2H,t), 6.02(2H,s), 7.34(2H,d), 7.48(2H,d), 7.9-8.1(2H,m), 8.1-8.3(2H,m)
198	3,4-Cl	-	6	F+: 431
199	2-OMe	-	6	F: 391
200	3-OMe	-	6	F: 391
201	4-OMe	-	6	F: 391
202	4-Ph	-	6	F: 437
203	3-CN	-	6	F: 386
204	4-CN	-	6	F: 386
205	4-SO_2NH_2	-	6	F: 440
206	4-CF_3	-	6	F: 429
207	4-F	-	6	F: 379 N1: 2.87(3H,s), 3.24(3H,s), 3.79(2H,t), 4.87(2H,t), 6.03(2H,s), 7.1-7.6(4H,m), 7.9-8.1(2H,m), 8.1-8.3(2H,m)
208	4-Br	-	6	F: 439, 441
209	3-CH_2NH_2	HCl	6	F: 390
210	4-CH_2NH_2	HCl	6	F: 390
211	3-NO_2	-	6	F: 406
212	4-NO_2	-	6	F: 406 N1: 2.87(3H,s), 3.26(3H,s), 3.81(2H,t), 4.89(2H,t), 6.18(2H,s), 7.61(2H,d), 7.9-8.4(6H,m)

表２０



(If)

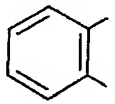
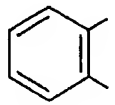
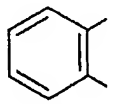
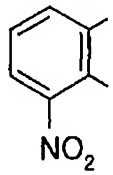
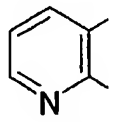
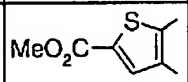
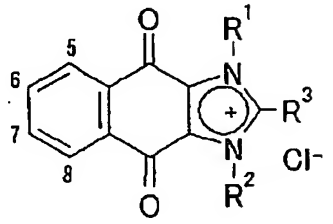
Ex	A	-R^2	-R^3	Sal	Sy	Dat
213		-Me	-CH_2OMe	-	6	F: 315
214		-Me	-CH_2NMe_2	HCl	6	F: 328
215		-$(CH_2)_4$-		-	6	F: 311
216		-$(CH_2)_2OMe$	-Me	-	6	F: 374 N1: 2.90(3H,s), 3.72(2H,t), 3.77(2H,t), 4.81(2H,t), 4.87(2H,t), 8.1-8.5(3H,m)
217		-$(CH_2)_2OMe$	-Me	HCl	6	F: 330
218		-$(CH_2)_2OMe$	-Me	-	6	F: 393

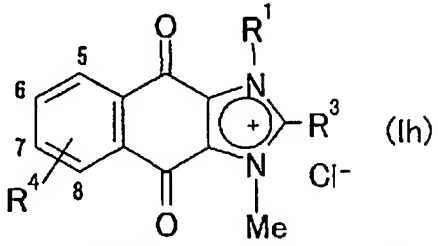
表２１



(Ig)

Co	R^1	R^2	R^3	Co	R^1	R^2	R^3
1	$-CH_2CH=CHCH_2OMe$	$-(CH_2)_2N(Bn)_2$	Me	18	$-(CH_2)_2OMe$	$-(CH_2)_2N(Me)COPh$	Me
2	$-(CH_2)_2OMe$	$-CH(Ph)CO_2Et$	Me	19	Me	$-(CH_2)_2NO_2$	Me
3	$-(CH_2)_2OMe$	$-(CH_2)_2SO_2NH_2$	Me	20	$-(CH_2)_2OMe$	$-(CH_2)_2CN$	Me
4	Me	$-(CH_2)_2SCH_2Ph$	Me	21	$-(CH_2)_2OMe$	$-CH_2COPh$	Me
5	$-(CH_2)_2OMe$	$-(CH_2)_2CO_2H$	Me	22	$-(CH_2)_2OMe$	$-CH_2CONH_2$	Me
6	$-(CH_2)_2OMe$	$-(CH_2)_2CO(Pyr)$	Me	23	$-(CH_2)_2OMe$	$-(CH_2)_2OAc$	Me
7	$-(CH_2)_2OMe$	$-(CH_2)_2CONH_2$	Me	24	Me	$-(CH_2)_2Ac$	Me
8	$-(CH_2)_2OMe$	$-(CH_2)_2N[(CH_2)_2NMe_2]_2$	Me	25	$-(CH_2)_2NH(CH_2)_2NH_2$	$-(CH_2)_2N(Me)Bn$	Me
9	$-(CH_2)_2OMe$	$-(CH_2)_2O(CH_2)_2NH(CH_2)_2NMe_2$	Me	26	$-(CH_2)_2OMe$	$-(CH_2)_2NHSO_2Me$	Me
10	$-(CH_2)_2OMe$	$-(CH_2)_2O(Py4)$	Me	27	$-(CH_2)_2OMe$	$-(CH_2)_2CONHOMe$	Me
11	$-CH_2C\equiv CCH_2OMe$	$-(CH_2)_2NHCONH_2$	Me	28	$-(CH_2)_2OMe$	$-(CH_2)_2OCOCH_2CO_2Et$	Me
12	$-(CH_2)_2OMe$	$-(CH_2)_2CO_2Me$	Me	29	Me	$-(CH_2)_2SOMe$	Me
13	$-(CH_2)_2OMe$	Me	CF_3	30	$-(CH_2)_2OMe$	Me	c-Pr
14	$-CH_2(Pyr)$	$-(CH_2)_2OMe$	H	31	Me	$-(CH_2)_2OMe$	$-(CH_2)_2OMe$
15	$-(CH_2)_2OMe$	$-(CH_2)_2O(CH_2)_2NMe_2$	Me	32	$-(CH_2)_2OMe$	$-(CH_2)_3O(CH_2)_2NMe_2$	Me
16	$-(CH_2)_2O$(c-Pr)	$-(CH_2)_2OMe$	Me	33	$-(CH_2)_2O-(CH_2)_2$(Morp)	$-(CH_2)_2OMe$	Me
17	$-(CH_2)_2OMe$	$-(CH_2)_2OCH_2-$		34	$-(CH_2)_2OMe$	$-(CH_2)_2N(Me)CH_2-$	

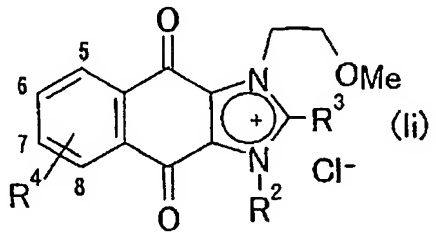
表２２



(Ih)

Co	R^1	R^3	R^4	Co	R^1	R^3	R^4
35	-CH_2(Py4)	Me	7-CF_3	37	-CH_2(Pyr)	H	6-NMe_2
36	-CH_2(Py3)	Me	5-CH_2NH_2	38	-$(CH_2)_2$OMe	Me	5-NO_2

表２３

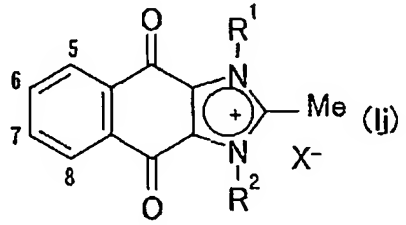


(Ii)

Co	R^2	R^3	R^4	Co	R^2	R^3	R^4
39	-CH_2(Pyr)	Me	5-F	57	-CH_2(Py4)	i-Pr	5-OMe
40	-CH_2(Py4)	Me	6-F	58	-CH_2(Py3)	Me	6-OMe
41	-$(CH_2)_2$OMe	Me	7-F	59	-CH_2(Pyr)	Me	7-OMe
42	-CH_2(Py3)	H	8-F	60	-$(CH_2)_2$OMe	Me	8-OMe
43	-CH_2(Pyr)	Me	8-CN	61	-CH_2(Py4)	Me	5-CN
44	-CH_2(Py3)	Me	5-CF_3	62	-CH_2(Py3)	Et	6-CN
45	-$(CH_2)_2$OMe	Et	6-CF_3	63	-$(CH_2)_2$OMe	Me	7-CN
46	-$(CH_2)_2$OMe	Me	5,8-OH	64	-CH_2(Pyr)	Me	8-CF_3
47	-CH_2(Py4)	Me	8-CH_2NH_2	65	-$(CH_2)_2$OMe	Me	5-CH_2N(Me)Bn
48	-CH_2(Py4)	Me	7-Me	66	-$(CH_2)_2$OMe	H	6-CH_2NH_2
49	-CH_2(Py3)	Me	8-Me	67	-CH_2(Pyr)	Me	7-CH_2NH_2
50	-$(CH_2)_2$OMe	Me	7-NMe_2	68	-CH_2(Py4)	Me	6-Me,7-F
51	-CH_2(Py4)	Me	8-NMe_2	69	-CH_2(Py3)	Me	5-NMe_2
52	-CH_2(Pyr)	Me	6,7-diMe	70	-$(CH_2)_2$OMe	Me	5,8-OMe

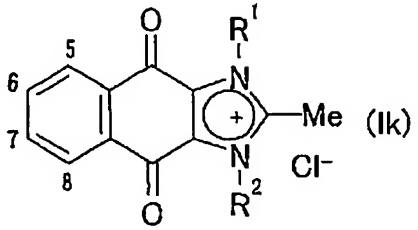
52	-CH_2(Pyr)	Me	6,7-diMe	70	-$(CH_2)_2$OMe	Me	5,8-OMe
53	-CH_2(Py4)	H	6-NO_2	71	-$(CH_2)_2$OMe	Me	5-CH_2N(Me)COPh
54	-$(CH_2)_2$OMe	Me	5-Me	72	-CH_2(Py3)	Me	7-NO_2
55	-CH_2(Pyr)	i-Pr	6-Me	73	-CH_2(Pyr)	Me	8-NO_2
56	-$(CH_2)_2$OMe	Me	5-CH_2NMe_2	74	-$(CH_2)_2$OMe	Me	5-CH_2(Morp)

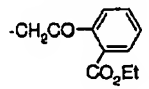
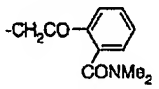
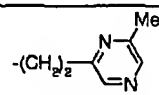
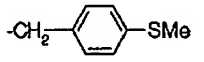
表２４



Co	R^1	R^2	X	Co	R^1	R^2	X
75	-CH_2(Pyr)	-$(CH_2)_2$OMe	Br	81	-CH_2(Pyr)	-$(CH_2)_2CO_2^-$	-
76	-CH_2(Py3)	-$(CH_2)_2$OMe	Br	82	-CH_2(Py4)	-$(CH_2)_2CO_2^-$	-
77	-CH_2(Py4)	-$(CH_2)_2$OMe	AcO	83	-CH_2(Py3)	-$CH_2CO_2^-$	-
78	-CH_2(Pyr)	-$(CH_2)_2$OMe	AcO	84	-$(CH_2)_2$OMe	-$CH_2CO_2^-$	-
79	-CH_2(Py3)	-$(CH_2)_2$OMe	$PhSO_3$	85	-CH_2(Py4)	-$(CH_2)_2$OMe	I
80	-$(CH_2)_2$OMe	-$(CH_2)_2$OMe	$PhSO_3$	86	-$(CH_2)_2$OMe	-$(CH_2)_2$OMe	I

表２５



Co	R^1	R^2	Co	R^1	R^2
87	-$(CH_2)_2$OMe		104		-$(CH_2)_2$OMe
88		-$(CH_2)_2$OMe	105		-$(CH_2)_2$OMe

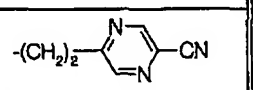
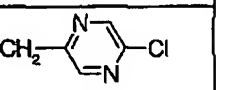
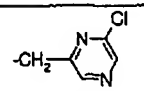
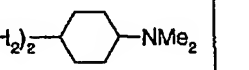
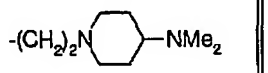
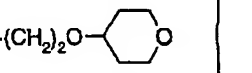
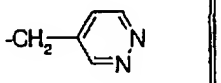
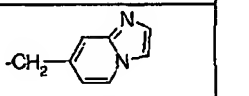
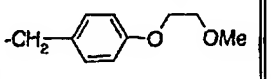
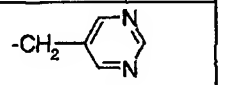
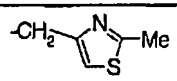
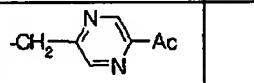
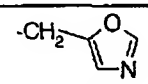
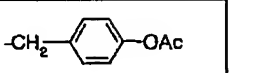
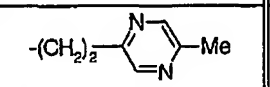
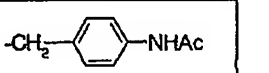
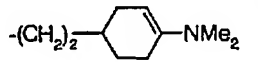
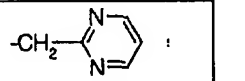
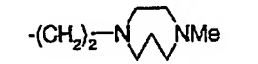
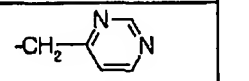
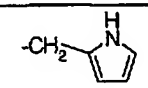
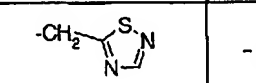
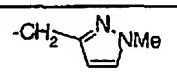
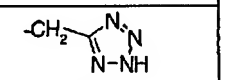
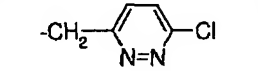
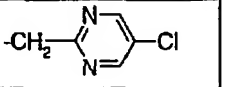
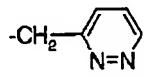
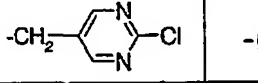
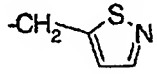
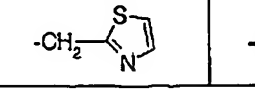
89	$-(CH_2)_2OMe$		106	$-(CH_2)_2OMe$	
90	$-(CH_2)_2OMe$		107	Me	
91	$-(CH_2)_2OMe$		108	$-(CH_2)_2OMe$	
92	$-(CH_2)_2OMe$		109	$-(CH_2)_2OMe$	
93	$-(CH_2)_2OMe$		110	$-(CH_2)_2OMe$	
94		$-(CH_2)_2OMe$	111		Me
95	$-(CH_2)_2OMe$		112	$-(CH_2)_2OMe$	
96	$-(CH_2)_2OMe$		113	$-(CH_2)_2OMe$	
97	$-(CH_2)_2OMe$		114	$-(CH_2)_2OMe$	
98	Me		115	$-(CH_2)_2OMe$	
99	$-(CH_2)_2OMe$		116		$-(CH_2)_2OMe$
100		$-(CH_2)_2OMe$	117	Me	
101	$-(CH_2)_2OMe$		118	$-(CH_2)_2OMe$	
102	$-(CH_2)_2OMe$		119		$-(CH_2)_2OMe$
103	Me		120		$-(CH_2)_2OMe$

表２６

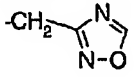
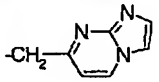
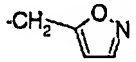
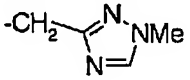
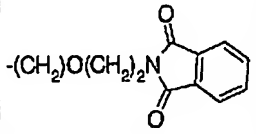
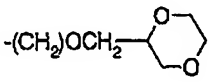
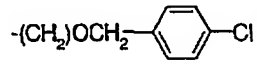
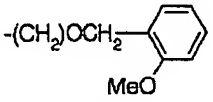
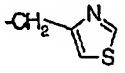
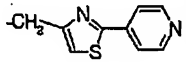
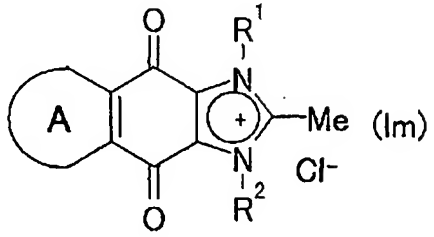
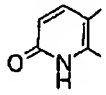
Co	R^1	R^2	Co	R^1	R^2
121		$-(CH_2)_2OMe$	126	$-(CH_2)_2OMe$	
122	$-(CH_2)_2OMe$		127	$-(CH_2)_2OMe$	
123	$-(CH_2)_2OMe$		128	$-(CH_2)_2OMe$	
124	$-(CH_2)_2OMe$		129	$-(CH_2)_2OMe$	
125	$-(CH_2)_2OMe$		130		$-(CH_2)_2OMe$

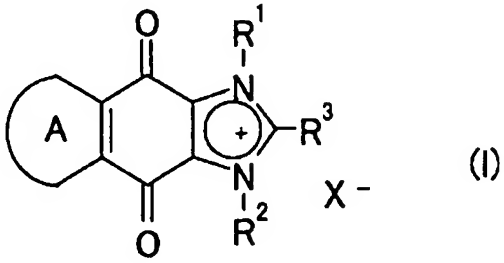
表２７



Co	R^1	R^2	A	Co	R^1	R^2	A
131	$-(CH_2)_2OMe$	$-(CH_2)_2OMe$		138	$-(CH_2)_2OMe$	$-(CH_2)_2OMe$	
132	$-(CH_2)_2OMe$	$-(CH_2)_2OMe$		139	$-(CH_2)_2OMe$	$-(CH_2)_2OMe$	
133	$-CH_2$(Py3)	$-(CH_2)_2OMe$		140	$-(CH_2)_2OMe$	$-CH_2$(Pyr)	
134	$-(CH_2)_2OMe$	$-(CH_2)_2OMe$		141	$-(CH_2)_2OMe$	$-(CH_2)_2OMe$	
135	$-CH_2$(Py3)	$-(CH_2)_2OMe$		142	$-CH_2$(Py4)	$-(CH_2)_2OMe$	
136	$-(CH_2)_2OMe$	$-(CH_2)_2OMe$		143	$-(CH_2)_2OMe$	$-(CH_2)_2OMe$	
137	$-(CH_2)_2OMe$	$-(CH_2)_2OMe$		144	$-(CH_2)_2OMe$	$-CH_2$(Py4)	

[Written Amendment]
[Filing Date] Heisei 14(2002) April 22 (2002. 4.22)
[Amendment 1]
[Document to be Amended] Description
[Item(s) to be Amended] Whole sentence
[Method of Amendment] Change

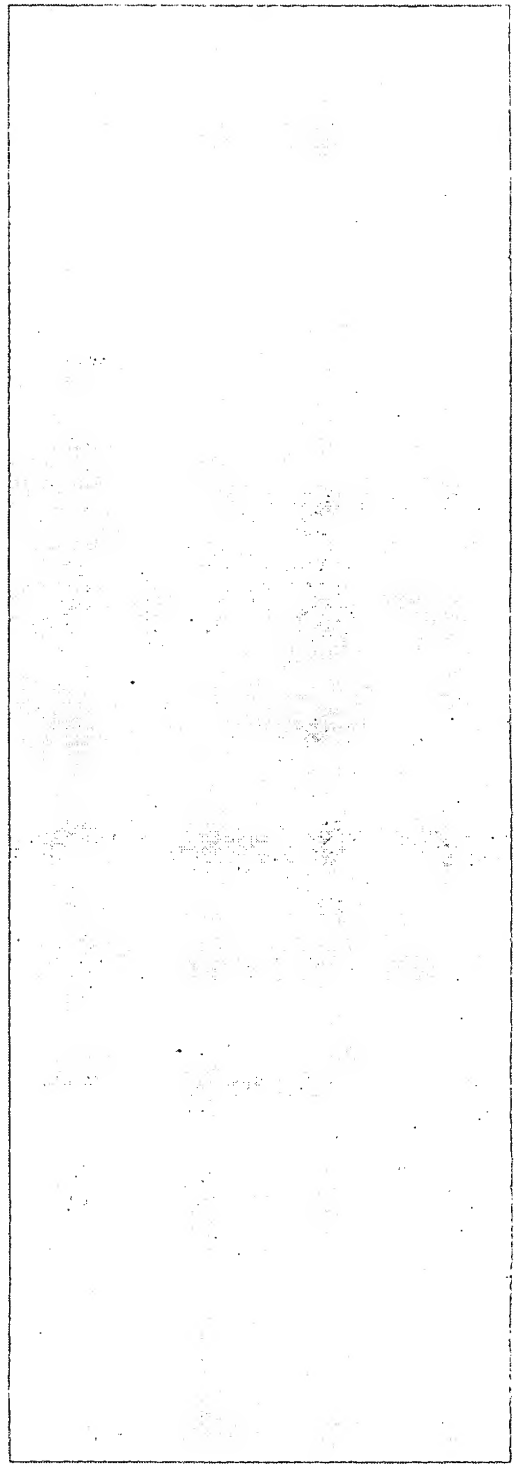
[The contents of amendment]
[Title of the Invention] Condensation imidazolium inductor
[Claim(s)]
[Claim 1] The condensation imidazolium inductor shown with a following general formula (I).
[Formula 1]

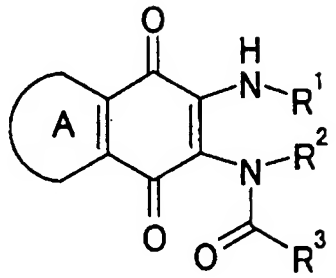


(I)

(The sign in a formula shows a following meaning.)
R1 and R2 : It is the same or different and - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (Low-grade alkynyl which has one or more substituents chosen from B group) - RinD, - low-grade alkyl, - low-grade ARUKENIRU, or - low-grade alkynyl, Either [at least] R1 or R2 However, - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (low-grade alkynyl which has one or more substituents chosen from B group), - (cycloalkyl which has one or more substituents), or - (5 which may have one or more substituents, or 7 member saturation heterocycle),
B group : -ORa, -SRa, OH formed into - prodrug, the -O-low-grade alkylene ORa, - The O-low-grade alkylene O-low-grade alkylene ORa, the -O-low-grade alkylene NRaRb, the -O-low-grade alkylene O-low-grade alkylene NRaRb, the -O-low-grade alkylene NRc-low-grade alkylene NRaRb, -OCO-NRaR
b, -SORa, -SO2Ra, -SO2NRaRb, -NRa-SO2Rb, -NRaRb
The -NRc-low-grade alkylene NRaRb, -N(- low-grade alkylene NRaRb)2
-RinD, -NO2, -CN, - halogen, -CO2Ra, -COO-, -CONRaRb, -CONRa-O-Rb, -NRa-CORb, -NRa-CO-NRbR
c, -OCORa, and -CO-Ra,
Ra, Rb, and Rc: It is the same or different and they are -H, - low-grade alkyl, the - low-grade alkylene RinD, or -RinD,
RinD: - (5 which may have one or more substituents, or 7 member saturation heterocycle), - (Cycloalkyl which may have one or more substituents) - (cyclo ARUKENIRU which may have one or more substituents), - (aryl which may have one or more substituents), or - (heteroaryl which may have one or more substituents),
R3:-H -- or (low-grade alkyl which may have one or more substituents) -- or -- the low-grade alkylene of carbon numbers 2 to 5 which R2 and R3 are united and may be interrupted for O, S, or NR4 (R4:-H or - low-grade alkyl) may be formed
A ring: -- the heteroaryl ring which may have the aryl ring which may have one or more substituents, or one or more substituents -- and
X-: When counter anion, however substituent-COO- of B group and imidazolium ion form inner salt, X- does not exist.
However, R1 and R2 remove the compound which are the following combination.
(1) One side is - low-grade alkylene (aryl which may have one or more substituents), and another side is -CH3, -(CH2)

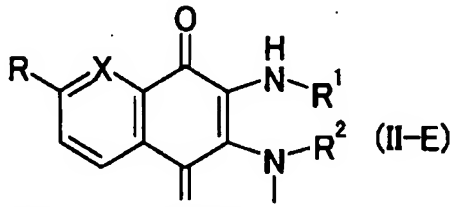
3CH3, or - phenyl,
(2) one side is - low-grade alkylene CO- (aryl which may have one or more substituents) -- another side -(CH2) 2CH(CH3) 2 or -(CH2) 3CH3 -- or
(3) Both R1 and R2 are - benzyl and -(CH2) 2OC2H5 or -(CH2) 2.
O-COCH3.
[Claim 2] The 1-[(6-chloro 3-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
1, the 2-dimethyl 4, 9-dioxo 3-[(2-tetrahydrofuranyl) methyl]-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
1, the 3-bis(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 1-(2-pyrazinyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-[3-(1H-4-imidazolyl) propyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
3-(2-methoxy ethyl)-2-methyl 1-[(5-methyl 2-pyrazinyl) methyl]-4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 2-methyl 4, 9-dioxo 1, 3-bis(2-pyrazinyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-[2-(2-methoxyethoxy) ethyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-{2-[2-(2-methoxyethoxy) ethoxy] ethyl}-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 3-(3-pyridyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 1-(2-pyridyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 1-(4-pyridyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-[(2-chloro 3-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-[(2-hydroxy 4-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 3-(2-methoxy ethyl)-1-[(6-methoxy 3-pyridyl) methyl]-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-[(2-chloro 4-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-(4-chloro benzyl)-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-(4-fluoro benzyl)-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
1, 3-bis(2-methoxy ethyl)-2-methyl 5-nitroglycerine 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU
Or these tautomers and the condensation imidazolium inductor of the claim 1 description chosen from a salt with a halogen ion.
[Claim 3] The 2-acylamino 3-amino 1 and 4-quinone derivative which are shown with a following general formula (II), or its salt.
[Formula 2]



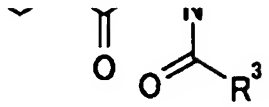


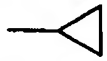
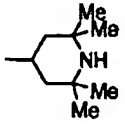
(II)

(The sign in a formula shows a following meaning.)
R1 and R2 : It is the same or different and - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (Low-grade alkynyl which has one or more substituents chosen from B group) - RinD, - low-grade alkyl, - low-grade ARUKENIRU, or - low-grade alkynyl, Either [at least] R1 or R2 However, - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (low-grade alkynyl which has one or more substituents chosen from B group), - (cycloalkyl which has one or more substituents), or - (5 which may have one or more substituents, or 7 member saturation heterocycle),
B group: -ORa, -SRa, OH formed into - prodrug, the -O-low-grade alkylene ORa, the -O-low-grade alkylene O-low-grade alkylene ORa, the -O-low-grade alkylene NRaRb, the -O-low-grade alkylene O-low-grade alkylene NRaRb
The -O-low-grade alkylene NRc-low-grade alkylene NRaRb, -OCO-NRa
The Rb, -SORa, -SO2Ra, -SO2NRaRb, -NRa-SO2Rb, -NRaRb, and -NRc-low-grade alkylene NRaRb, -N (- low-grade alkylene NRaRb)
2, -RinD, -NO2, -CN, - halogen, -CO2Ra, -CONRaRb
-CONRa-O-Rb, -NRa-CORb, -NRa-CO-NRbRc, -OCORa, and -CO-Ra,
Ra, Rb, and Rc: It is the same or different and they are -H, - low-grade alkyl, the - low-grade alkylene RinD, or -RinD,
RinD: - (5 which may have one or more substituents, or 7 member saturation heterocycle), - (Cycloalkyl which may have one or more substituents) - (cyclo ARUKENIRU which may have one or more substituents), - (aryl which may have one or more substituents), or - (heteroaryl which may have one or more substituents),
R3:-H -- or (low-grade alkyl which may have one or more substituents) -- or -- the low-grade alkylene of carbon numbers 2 to 5 which R2 and R3 are united and may be interrupted for O, S, or NR4 (R4:-H or - low-grade alkyl) may be formed -- and
A ring: The heteroaryl ring which may have the aryl ring which may have one or more substituents, or one or more substituents.
However, the compound of the following table is removed.
[Table 1]



(II-E)



Comp	X	R	-R¹	-R²	-R³
E-1	CH	H	-Me	-CH_2-(3,4-Cl-Ph)	-Me
E-2	CH	H	-$CH(Me)_2$	-CH_2-(3,4-Cl-Ph)	-Me
E-3	CH	H	-CH_2-Ph	-(4-MeO-Ph)	-Me
E-4	CH	H	-CH_2-Ph	-(3-Br-Ph)	-Me
E-5	CH	H	-CH_2-Ph	-CH_2-(4-F-Ph)	-Me
E-6	CH	H	-$(CH_2)_2$-Ph	-CH_2-(4-F-Ph)	-Me
E-7	CH	H	-$(CH_2)_2$-OH	-Me	-Me
E-8	CH	H	-$(CH_2)_2$-OH	-CH_2-Ph	-Me
E-9	CH	H	-$(CH_2)_2$-OH	-(4-MeO-Ph)	-Me
E-10	CH	H	-$(CH_2)_2$-OH	-(4-MeCO-Ph)	-Me
E-11	CH	H	-$(CH_2)_2$-OH	-(3-Br-Ph)	-Me
E-12	CH	H	-$(CH_2)_2$-Cl	-CH_2CO_2Et	-Me
E-13	CH	H	-CH(Me)-CO_2H	-Me	-Me
E-14	CH	H	-CH(Me)-CONHMe	-Me	-Me
E-15	CH	H	-CH(Me)-CONHMe	-$CH(Me)_2$	-Me
E-16	CH	H	-CH(Me)-CONHMe		-Me
E-17	CH	H	-CH(Me)-CONHMe	-Me	-$(CH_2)_2Me$
E-18	CH	H	-CH(Me)-CONHMe	-Me	-$CH(Me)_2$
E-19	CH	H	-CH(Me)-CONHOMe	-Me	-Me
E-20	N	H	-CH(Me)-CONHMe	-Me	-Me
E-21	N	Me	-CH(Me)-CONHMe	-Me	-Me
E-22	CH	H		-Me	-Me

(-- the inside of front, and Comp -- a compound number -- Me -- a methyl group -- Et -- an ethyl group -- Ph -- a phenyl group -- moreover, in the case of a substitution phenyl group, a substituent is shown with a substitution position before Ph, for example, 3 and 4-Cl-Ph shows 3 and 4-dichlorophenyl.)

[Claim 4] The condensation imidazole derivative shown with a following general formula (III), or its salt.

CONTINUE

For further translation, please click on the above button.
The current translation will be overwritten when you continue.

[Translation done.]

Report Mistranslation | Japanese (whole document in PDF)

[JP,01/060803,A1(2001)]

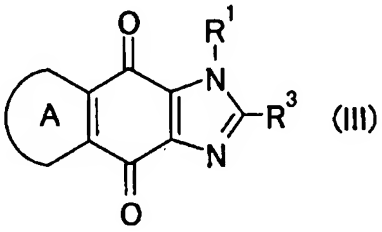
Japanese (PDF) | File Wrapper Information

FULL CONTENTS CLAIM + DETAILED DESCRIPTION WRITTEN AMENDMENT

[Translation done.]

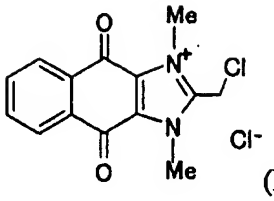
Continued translation.

[Formula 3]

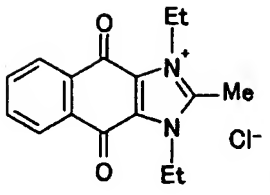


(The sign in a formula shows a following meaning.)
R1: - (low-grade alkyl which has one or more substituents chosen from B group) - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - Or - (cycloalkyl which has one or more substituents), (Low-grade alkynyl which has one or more substituents chosen from B group) However, the low-grade alkyl group which has one or more substituents chosen from the group which consists of -NH2, -NMe2, -NEt2, -OH, - halogen, and - (phenyl which may be replaced by -Cl, -F, -Me, or -OMe) is excluded,
B group : - ORa, -SRa, OH formed into - prodrug, the -O-low-grade alkylene ORa, - The O-low-grade alkylene O-low-grade alkylene ORa, the -O-low-grade alkylene NRaRb, the -O-low-grade alkylene O-low-grade alkylene NRaRb, the -O-low-grade alkylene NRc-low-grade alkylene NRaRb, -OCO-NRaRb, -SORa, -SO2Ra, -SO2NRaRb, -NRa-SO2Rb, -NRaRb
The -NRc-low-grade alkylene NRaRb, -N(- low-grade alkylene NRaRb)2
-RinD, -NO2, -CN, - halogen, -CO2Ra, -CONRaRb, -CONRa-O-Rb, -NRa-CORb, -NRa-CO-NRbRc, -OCORa, and -CO-Ra,
Ra, Rb, and Rc: It is the same or different and they are -H, - low-grade alkyl, the - low-grade alkylene RinD, or -RinD,
RinD: - (5 which may have one or more substituents, or 7 member saturation heterocycle) - (Cycloalkyl which may have one or more substituents) - (cyclo ARUKENIRU which may have one or more substituents), - (aryl which may have one or more substituents), or - (heteroaryl which may have one or more substituents),
R3:-H -- or (low-grade alkyl which may have one or more substituents) -- and
A ring: Heteroaryl ring which may have the aryl ring which may have one or more substituents, or one or more substituents.
[Detailed Description of the Invention]
[0001]
[Field of the Invention]
This invention relates to medicine, a new condensation imidazolium inductor especially useful for the therapy of cancer, and its new manufacture intermediate product compound.
[0002]
[Description of the Prior Art]
As the aryl ring or heteroaryl ring which has antitumor activity conventionally, and the condensed imidazolium inductor, 4 of bottom type and 9-dioxo [2 and 3-naphth d] imidazolium compound (KP-1, KP-3 grade) is [only being indicated by Khim.Pharm.Zh., 32 (6), and 10-11 (1998) and].
[Formula 4]

[Translation done.]

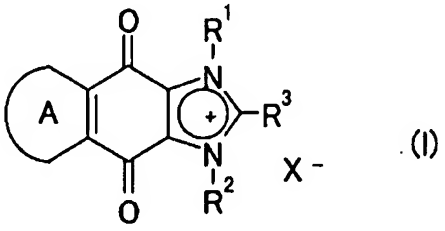


(KP-1)



(KP-3)

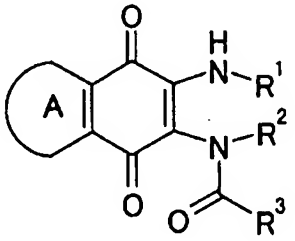
(Et shows ethyl among a formula and Me shows methyl, respectively.) the following -- the same .
J. In Med.Chem., 7 (3), and 362-364 (1964), it is the general formula (I) smell of after-mentioned this invention.
Both **, and R1 and R2 are low-grade alkyl, or one side is - low-grade alkylene (aryl which may have one or more substituents), and another side is -CH3. - (CH2)
3CH3, the compound which is - phenyl group, or one side is - low-grade alkylene CO- (aryl which may have one or more substituents), and another side - (CH)
2) There are 2CH(CH3)2 or -(CH2) 3CH3, and an indication of a compound that comes out and has a certain antimicrobial action. However, there is no indication about an anticancer operation.
[0003]
Furthermore, in [J.Org.Chem.USSR, 1, 1479-85 (1965) JP,H3-258765,A, JP,H6-59371,A, etc.] the general formula (I) of after-mentioned this invention, 4 and 9-dioxo [2 and 3-naphth d] imidazolium inductor both R1 and whose R2 are low-grade alkyl groups is indicated. However, there is no indication about the medicine use of these compounds.
[0004]
The indication of isoquinoline 5 useful as an herbicide and 8-dione inductor has useful as herbicide 1, 4-dihydro1, and 4-dioxo naphthalene inductor in the British Patent No. 1314881 gazette at Japanese patent JP,S54-25085,B, respectively. Moreover, some 1, 4-dihydro1, and 4-dioxo naphthalene inductors are Zh. Org.Khim. and 22 (8), 1736-42 J.Gen.Chem.USSR, 36, and 649-652 (1966), (1986) And it is well-known by a reagent catalog [Sigma Aldrich Library of Rare Chemicals Structure Index, with update (Aldrich Chemical Company, Inc.), etc.]. However, about the medicine use of these compounds, there is all no indication.
WO 97/No. 30022 gazette, J.Med.Chem.39, 1447-1451 (1996) and J.Med.Chem., 7 (3), and 362-364 (1964) have the indication of an aryl ring and the condensed imidazole derivative.
[0005]
[Problem(s) to be Solved by the Invention]
It has a good anticancer operation and is still anxious for the invention of the anticancer agent which is moreover low toxicity.
[0006]
[Means for Solving the Problem]
It is characterized by replacing the 1st place and/or the 3rd place by the alkyl group which has a substituent, as a result of this invention person's etc. taking lessons from an anticancer agent with few side reactions and inquiring wholeheartedly. While a new aryl ring or a heteroaryl ring, and the condensed imidazolium inductor have good antitumor activity, it is low toxicity, and it found out that it could become the large anticancer agent of a safety margin. Moreover, the 2-acylamino 3-amino 1 useful as these manufacture intermediate products, 4-quinone derivative, and a condensation imidazole derivative are found out. Furthermore, the 2-acylamino 3-amino 1 and the 4-quinone derivative itself which is this manufacture intermediate product also carry out the knowledge of having good antitumor action by low toxicity, and completes this invention.
[0007]
That is, this invention relates to the condensation imidazolium inductor shown with a following general formula (I), and the condensation imidazolium inductor concerned.
[Formula 5]



(I)

(The sign in a formula shows a following meaning.)
R1 and R2 : It is the same or different and - (low-grade alkyl which has one or more substituents chosen

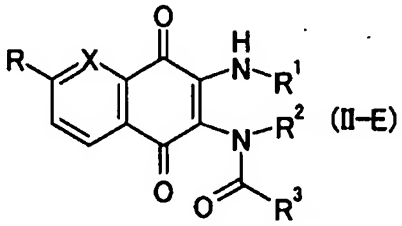
from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (Low-grade alkynyl which has one or more substituents chosen from B group) - RinD, - low-grade alkyl, - low-grade ARUKENIRU, or - low-grade alkynyl, Either [at least] R1 or R2 However, - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (low-grade alkynyl which has one or more substituents chosen from B group), - (cycloalkyl which has one or more substituents), or - (5 which may have one or more substituents, or 7 member saturation heterocycle),
B group : -ORa, -SRa, OH formed into - prodrug, the -O-low-grade alkylene ORa, - The O-low-grade alkylene O-low-grade alkylene ORa, the -O-low-grade alkylene NRaRb, the -O-low-grade alkylene O-low-grade alkylene NRaRb, the -O-low-grade alkylene NRc-low-grade alkylene NRaRb, -OCO-NRaR b, -SORa, -SO2Ra, -SO2NRaRb, -NRa-SO2Rb, -NRaRb
The -NRc-low-grade alkylene NRaRb, -N(- low-grade alkylene NRaRb)2
-RinD, -NO2, -CN, - halogen, -CO2Ra, -COO-, -CONRaRb, -CONRa-O-Rb, -NRa-CORb, -NRa-CO-NRbR
c, -OCORa, and -CO-Ra,
Ra, Rb, and Rc: It is the same or different and they are -H, - low-grade alkyl, the - low-grade alkylene RinD, or -RinD,
RinD: - (5 which may have one or more substituents, or 7 member saturation heterocycle), - (Cycloalkyl which may have one or more substituents) - (cyclo ARUKENIRU which may have one or more substituents), - (aryl which may have one or more substituents), or - (heteroaryl which may have one or more substituents),
R3: You may form the low-grade alkylene of carbon numbers 2 to 5 which -H, - (low-grade alkyl which may have one or more substituents), or R2 and R3 are united, and may be interrupted for O, S, or NR4 (R4:-H or - low-grade alkyl),
A ring: -- the heteroaryl ring which may have the aryl ring which may have one or more substituents, or one or more substituents -- and
X-: When counter anion, however substituent-COO- of B group and imidazolium ion form inner salt, X- does not exist.
However, R1 and R2 remove the compound which are the following combination.
(1) One side is - low-grade alkylene (aryl which may have one or more substituents), and another side is - CH3, -(CH2) 3CH3, or - phenyl,
(2) one side is - low-grade alkylene CO- (aryl which may have one or more substituents) -- another side - (CH2) 2CH(CH3)2 or -(CH2) 3CH3 -- or
(3) Both R1 and R2 are - benzyl and -(CH2) 2OC2H5 or -(CH2) 2 O-COCH3. the following -- the same .
[0008]
Moreover, this invention is the manufacture intermediate product of the above-mentioned general formula (I), and, also in itself, relates to the 2-acylamino 3-amino 1 and 4-quinone derivative which are shown with the following general formula (II) which has a good anticancer operation, or its salt.
[Formula 6]

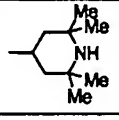


(II)

(The sign in a formula shows a following meaning.)
R1 and R2 : It is the same or different and - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (Low-grade alkynyl which has one or more substituents chosen from B group) - RinD, - low-grade alkyl, - low-grade ARUKENIRU, or - low-grade alkynyl, Either [at least] R1 or R2 However, - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (low-grade alkynyl which has one or more substituents chosen from B group), - (cycloalkyl which has one or more substituents), or - (5 which may have one or more substituents, or 7 member saturation heterocycle),
B group : -ORa, -SRa, OH formed into - prodrug, the -O-low-grade alkylene ORa, - The O-low-grade alkylene O-low-grade alkylene ORa, the -O-low-grade alkylene NRaRb, the -O-low-grade alkylene O-low-grade alkylene NRaRb, the -O-low-grade alkylene NRc-low-grade alkylene NRaRb, -OCO-NRaR

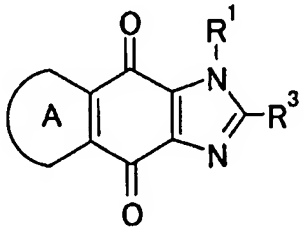
b, -SORa, -SO2Ra, -SO2NRaRb, NRa-SO2Rb, - The NRaRb and -NRc-low-grade alkylene NRaRb, -N (- low-grade alkylene NRaRb)2, -RinD, - NO2, -CN, - halogen, -CO2Ra, -CONRaRb, -CONRa-O-Rb, - NRa-CORb, -NRa-CO-NRbRc, -OCORa, and -CO-Ra,
Ra, Rb, and Rc: It is the same or different and they are -H, - low-grade alkyl, the - low-grade alkylene RinD, or -RinD,
RinD: - (5 which may have one or more substituents, or 7 member saturation heterocycle), - (Cycloalkyl which may have one or more substituents) - (cyclo ARUKENIRU which may have one or more substituents), - (aryl which may have one or more substituents), or - (heteroaryl which may have one or more substituents),
the low-grade alkylene of carbon numbers 2 to 5 which R3:-H, - (low-grade alkyl which may have one or more substituents), or R2 and R3 are united, and may be interrupted for O, S, or NR4 (R4:-H or - low-grade alkyl) may be formed -- and
A ring: The heteroaryl ring which may have the aryl ring which may have one or more substituents, or one or more substituents.
However, the compound of the following table is removed.
[0009]
[Table 2]



Comp	X	R	-R1	-R2	-R3
E-1	CH	H	-Me	-CH2-(3,4-Cl-Ph)	-Me
E-2	CH	H	-CH(Me)2	-CH2-(3,4-Cl-Ph)	-Me
E-3	CH	H	-CH2-Ph	-(4-MeO-Ph)	-Me
E-4	CH	H	-CH2-Ph	-(3-Br-Ph)	-Me
E-5	CH	H	-CH2-Ph	-CH2-(4-F-Ph)	-Me
E-6	CH	H	-(CH2)2-Ph	-CH2-(4-F-Ph)	-Me
E-7	CH	H	-(CH2)2-OH	-Me	-Me
E-8	CH	H	-(CH2)2-OH	-CH2-Ph	-Me
E-9	CH	H	-(CH2)2-OH	-(4-MeO-Ph)	-Me
E-10	CH	H	-(CH2)2-OH	-(4-MeCO-Ph)	-Me
E-11	CH	H	-(CH2)2-OH	-(3-Br-Ph)	-Me
E-12	CH	H	-(CH2)2-Cl	-CH2CO2Et	-Me
E-13	CH	H	-CH(Me)-CO2H	-Me	-Me
E-14	CH	H	-CH(Me)-CONHMe	-Me	-Me
E-15	CH	H	-CH(Me)-CONHMe	-CH(Me)2	-Me
E-16	CH	H	-CH(Me)-CONHMe		-Me
E-17	CH	H	-CH(Me)-CONHMe	-Me	-(CH2)2Me
E-18	CH	H	-CH(Me)-CONHMe	-Me	-CH(Me)2
E-19	CH	H	-CH(Me)-CONHOMe	-Me	-Me
E-20	N	H	-CH(Me)-CONHMe	-Me	-Me
E-21	N	Me	-CH(Me)-CONHMe	-Me	-Me
E-22	CH	H		-Me	-Me

(the inside of front, and Comp -- a compound number -- Me -- a methyl group -- Et -- an ethyl group -- Ph -- a phenyl group -- moreover, in the case of a substitution phenyl group, a substituent is shown with a substitution position before Ph, for example, 3 and 4-Cl-Ph shows 3 and 4-dichlorophenyl.) the

following -- the same .
[0010]
The British Patent No. 1314881 gazette and Japanese patent JP,S54-25085,B concerning [the above and the compound shown in Table 2] an herbicide, Literature Zh.Org.Khim. about a synthetic process, 22 (8), 1736-42 And J.Gen.Chem.USSR, 36, and 649-652 (1966), (1986) And it is well-known by a reagent catalog [Sigma Aldrich Library of Rare Chemicals Structure Index, with update (Aldrich Chemical Company, Inc.), etc.].
[0011]
Furthermore, this invention relates to the condensation imidazole derivative which is a new manufacture intermediate product of the above-mentioned general formula (I) and which is shown with a following general formula (III), or its salt.
[Formula 7]



(The sign in a formula shows a following meaning.)
R1: - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - Or - (cycloalkyl which has one or more substituents), (Low-grade alkynyl which has one or more substituents chosen from B group) However, the low-grade alkyl group which has one or more substituents chosen from the group which consists of -NH2, -NMe2, -NEt2, -OH, - halogen, and - (phenyl which may be replaced by -Cl, -F, -Me, or -OMe) is excluded,
B group : -ORa, -SRa, OH formed into - prodrug, the -O-low-grade alkylene ORa, - The O-low-grade alkylene O-low-grade alkylene ORa, the -O-low-grade alkylene NRaRb, the -O-low-grade alkylene O-low-grade alkylene NRaRb, the -O-low-grade alkylene NRc-low-grade alkylene NRaRb, -OCO-NRaRb, -SORa, -SO2Ra, -SO2NRaRb, -NRa-SO2Rb, -NRaRb
The -NRc-low-grade alkylene NRaRb, -N(- low-grade alkylene NRaRb)2
-RinD, -NO2, -CN, - halogen, -CO2Ra, -CONRaRb, -CONRa-O-Rb, -NRa-CORb, -NRa-CO-NRbRc, -OCORa, and -CO-Ra,
Ra, Rb, and Rc: It is the same or different and they are -H, - low-grade alkyl, the - low-grade alkylene RinD, or -RinD,
RinD: - (5 which may have one or more substituents, or 7 member saturation heterocycle), - (Cycloalkyl which may have one or more substituents) - (cyclo ARUKENIRU which may have one or more substituents), - (aryl which may have one or more substituents), or - (heteroaryl which may have one or more substituents),
R3: -H or - (low-grade alkyl which may have one or more substituents),
A ring: The heteroaryl ring which may have the aryl ring which may have one or more substituents, or one or more substituents. the following -- the same .
[0012]
[Embodiment of the Invention]
A general formula (I) and the compound which (II) Reaches (III) are explained further.
The word "low-grade" Becoming means the hydrocarbon chain of the shape of a straight chain of 1-6 carbon numbers, or the letter of branching among this Description. As "low-grade alkyl", it is the alkyl group of 1 to 4 carbon numbers preferably, and they are methyl, ethyl, n-propyl, isopropyl, n-butyl, and an isobutyl machine especially preferably. As "low-grade ARUKENIRU", they are vinyl, an allyl compound, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, and 3-butenyl group preferably. As "low-grade alkynyl", they are ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, and 1-methyl 2-propynyl group preferably. Moreover, as a "low-grade alkylene", it is methylene, ethylene, trimethylene and 2, and 2-dimethyl trimethylene machine preferably.
As "aryl", an aromatic hydrocarbon ring machine is meant, and the aryl group of 6 to 14 carbon numbers is desirable, and are a phenyl, naphthyl, and a fluorenyl group preferably. Moreover, as an "aryl ring" in A ring, it is the ring which forms said aryl group, and they are benzene and a naphthalene ring preferably.
[0013]
5 which contains as "heteroaryl" 1 to 4 hetero atoms chosen from N, S, and O or 6 member monocycle

heteroaryl group, and these are benzene-ring or 5 to 6 member monocycle heteroaryl and condensed 2 ring type heteroaryl group, and may be saturated partially. Moreover, when N atom is included, you may form N-oxide. Here as 5 to 6 member monocycle heteroaryl A furil, thienyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, Iso thiazolyl, oxazolyl, iso oxazolyl, oxadiazolyl, Thiadiazolyl, triazoryl, tetra-ZORIRU, pyridyl, pyrimidinyl, pilus DAJINIRU, pyrazinyl ones, and a thoriadinyl group are desirable, and as 2 ring type heteroaryl Benzofuranyl one, benzothienyl, benzothiadiazolyl, benzothiazolyl, Benzoxazolyl, benzooxadiazolyl, benzoimidazolyl, India Lil, iso India Lil, indazolyl, quinolyl, iso quinolyl, SHINNORINIRU, chinae-cortex ZORINIRU, KINOKISARINIRU, benzodioxolyl, in DORIJINIRU, and an imidazo pyridyl machine are desirable. As partial saturation heteroaryl, a 1, 2, 3, and 4-tetrahydro quinolyl machine etc. is mentioned. Furthermore, preferably, it is a furil, thienyl, imidazolyl, pyridyl, pyrazinyl one, pyrimidinyl, pilus DAJINIRU, India Lil, benzoimidazolyl, benzodioxo nil, and a quinolyl machine, and they are pyridyl, pyrazinyl one, and a pyrimidinyl group especially preferably.

[0014]

As a heteroaryl ring in A ring, are the ring which forms the above-mentioned heteroaryl group, are 5 to 6 member monocycle heteroaryl ring preferably, and still more preferably They are thiophene, Fran, a pyrrole, imidazole, oxazole, thiazole, a pyridine, pyrazine, and a pyrimidine ring.

As "cycloalkyl", it is the cycloalkyl machine of 3-10 carbon numbers preferably, and they are cyclo propyl, cyclopentyl, cyclohexyl, and an adamanthyl machine especially preferably. As "cyclo ARUKENIRU", it is the cyclo alkenyl group of 3-8 carbon numbers preferably, and they are cyclo pentenyl and a cyclohexenyl group especially preferably.

If it is anion pharmaceutically permitted as counter anion of imidazolium ion as "counter anion", there will be no restriction in particular and preferably a halogen ion and an organic-sulfonic-acid ion (for example, a methansulfonic acid ion --) Anion univalent [, such as acetate ions, such as an ethane-sulfonic-acid ion, a benzenesulfonic acid ion, and a toluenesulfonic acid ion, trifluoro acetate ion, carbonate ion, and sulfate ion,] or divalent is mentioned, and it is a halogen ion especially preferably. As "halogen", F, Cl, Br, and I atom are mentioned, and they are these ions as a "halogen ion." As "halogeno low-grade alkyl", said halogen is said low-grade alkyl replaced one or more, and is -CF3 preferably.

"5 to 7 member saturation heterocycle" is 5 containing 1 to 4 hetero atoms chosen from N, S, and O, 7 member monocycle saturation heterocycle, or its bridge ring. They are tetrahydropyranyl, tetrahydrofuranyl one, pyrrolidinyl, piperazinyl one, AZEPANIRU, JIAZEPANIRU, quinuclidinyl, piperidyl, and a mole HORINIRU machine preferably.

[0015]

"OH formed into - prodrug" is the group in which the reversible prodrug inductor restored to a parent compound (hydroxy compound of a yuan) in the living body was formed -- for example, Prog. It is the group indicated to Med.5:2157-2161 (1985). the low-grade alkylene COOR (R shows H or low-grade alkyl --) which may have a -OCO-substituent preferably The low-grade alkenylene COOR which may have a -OCO-substituent like the following - The aryl, the -OCO low-grade alkylene O-low-grade alkylene COOR which may have an OCO-substituent - The low-grade alkylene COOR which may have the low-grade alkyl and -OSO2-substituent which may have OCO-CO-R and a -OCO-substituent, -O-lid RIJIRU, the 5-methyl 1, 3-dioxo ****- 2-****- 4-****- methyloxy, etc. are mentioned.

[0016]

- - (cycloalkyl which may have one or more substituents), (5 which may have one or more substituents, or 7 member saturation heterocycle) - (Cyclo ARUKENIRU which may have one or more substituents) although there is no restriction in particular as a substituent in - (aryl which may have one or more substituents), or - (heteroaryl which may have one or more substituents) They are 1-4 substituents preferably chosen from following C group.

C group: The - low-grade alkyl, - halogen, - halogeno low-grade alkyl, -ORa, and -O-low-grade alkylene ORa, -SRa, -NRaRb, -NO2, -CN, -CO2

The Ra, -CO-NRaRb, -CORa, -NRa-CORb, -SO2NRaRb, and - low-grade alkylene NRaRb, - aryl, - low-grade alkylene aryl, and -OCO-Ra (Ra and Rb show the same meaning as the above among a formula).

A still more desirable group among said C group - low-grade alkyl, - halogen, - halogeno low-grade alkyl, - OH, -O-low-grade alkyl, the -O-low-grade alkylene OH, -O-low-grade alkylene O-low-grade alkyl, - They are low-grade alkylene NH2, -NH2, -NH-low-grade alkyl, -N(low-grade alkyl)2, and - CO2H, -CO2-low-grade alkyl, -CO-NH2, -SO2-NH2, -NO2, and -CN. the following -- the same .

As a substituent in "the aryl ring which may have one or more substituents" in A ring, or "the heteroaryl ring which may have one or more substituents", preferably, the group of said C group is mentioned and a still more desirable group is the same as that of the above. It is -NO2 especially preferably.

[0017]

Although there is no restriction in particular as a substituent in "the low-grade alkyl which may have one or more substituents" of R3, it is the substituent of said B group preferably, and they are - halogen, -

ORa, -SRa, -NRaRb, -NO2, and -CN still more preferably.
In addition, in said B group and C group, the group Ra, Rb, and whose Rc are -H or - low-grade alkyl is more desirable as a group shown using Ra, Rb, and Rc.
["forming the low-grade alkylene of carbon numbers 2 to 5 which R2 and R3 are united and may be interrupted for O, S, or NR4 (R4:-H or - low-grade alkyl)"] The low-grade alkylene chain (preferably - (CH2) 4-, - (CH2) 2OCH2- and -(CH2) 2N(Me) CH2-) which may be interrupted for O, S, or NR4 which R2 and R3 form, and its next door
It means touching N and C atom being united, and forming 4 to 7 member heterocycle.
[0018]
In this invention compound (I) or (II), it is a desirable compound,
Either [at least] R1 or R2 (1) - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (Low-grade alkynyl which has one or more substituents chosen from B group) - (Cycloalkyl which has one or more substituents chosen from C group) [or -(5 which may have one or more substituents chosen from C group, or 7 member saturation heterocycle);RinD] - (5 which may have one or more substituents chosen from C group, or 7 member saturation heterocycle) - (Cycloalkyl which may have one or more substituents chosen from C group) - (Cyclo ARUKENIRU which may have one or more substituents chosen from C group) - (Aryl which may have one or more substituents chosen from C group) [- (heteroaryl which may have one or more substituents chosen from C group);R3 / or] - The low-grade alkylene of carbon numbers 2 to 5 which H, - (low-grade alkyl which may have one or more substituents chosen from B group), or R2 and R3 are united, and may be interrupted for O, S, or NR4 (R4:-H or - low-grade alkyl) may be formed, and;A ring, The compound which is the heteroaryl ring which may have one or more substituents chosen from the aryl ring or C group which may have one or more substituents chosen from C group,
(2) The compound which is low-grade alkyl in which either [at least] R1 or R2 have one or more substituents chosen from B group,
(3) The compound which is low-grade alkyl which has one or more substituents which both R1 and R2 are the same or different, and are chosen from B group,
(4) Either [at least] R1 or R2 are -ORa, -NRaRb, and -NRa-COR.
The b and -O-low-grade alkylene ORa, the -O-low-grade alkylene O-low-grade alkylene ORa, - SRa, - CONRaRb, -CN, - (cycloalkyl which may have one or more substituents chosen from C group), - (5 which may have one or more substituents chosen from C group, or 7 member saturation heterocycle) - (Aryl which may have one or more substituents chosen from C group) And the compound which is low-grade alkyl which has one or more substituents chosen from the group which consists of - (heteroaryl which may have one or more substituents chosen from C group),
(5) Either [at least] R1 or R2 are -ORa and the -O-low-grade alkylene ORa.
The -O-low-grade alkylene O-low-grade alkylene ORa, - (5 which may have one or more substituents chosen from C group, or 7 member saturation heterocycle), - (Aryl which may have one or more substituents chosen from C group) And the compound which is low-grade alkyl which has one or more substituents chosen from the group which consists of - (heteroaryl which may have one or more substituents chosen from C group),
(6) Either [at least] R1 or R2 may have one or more substituents chosen from C group. The compound which is low-grade alkyl replaced by the heteroaryl group chosen from (a furil, thienyl, imidazolyl, pyridyl, pyrazinyl ones, pyrimidinyl, pilus DAJINIRU, India Lil, benzoimidazolyl, benzodioxo nil, and a quinolyl machine),
(7) Either R1 or R2 are low-grade alkyl replaced by -O-low-grade alkyl. Another side -O-low-grade alkylene O-low-grade alkyl and -O-low-grade alkylene O-low-grade alkylene O-low-grade alkyl, - (Aryl which may have one or more substituents chosen from C group) The compound which is low-grade alkyl which has one substituent chosen from the group which consists of - (heteroaryl which may have one or more substituents chosen from C group), and -O-low-grade alkyl,
(8) either [at least] R1 or R2 - (you may have one or more substituents chosen from C group --) The compound which is low-grade alkyl which has one substituent chosen from the group which consists of heteroaryl, -O-low-grade alkylene O-low-grade alkyl, and -O-low-grade alkyl which are chosen from pyridyl, pyrazinyl ones, and a pyrimidinyl group,
(9) The compound whose R3 is a methyl group,
(10) A ring may have one or more substituents chosen from benzene ring or C group which may have one or more substituents chosen from C group. The compound which is the heteroaryl ring chosen from thiophene, Fran, a pyrrole, imidazole, oxazole, thiazole, a pyridine, pyrazine, pyridazine, and a pyrimidine ring,
(11) the compound which is benzene ring by which A ring may be replaced by -NO2 -- or
(12) X- is the compound which is a halogen ion.
[0019]

[moreover, desirable compound with the another this invention compound (I)] R1 and R2 are the same or different, and - (low-grade alkyl which has one or more substituents chosen from B' group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B' group) - (Low-grade alkynyl which has one or more substituents chosen from B' group) - (Cycloalkyl which may have one or more substituents chosen from C' group) - (5 or 6 member monocycle heteroaryl which may have one or more substituents chosen from C' group) - (Aryl which may have one or more substituents chosen from C' group) - (5 or 7 member saturation heterocycle which may have one or more substituents chosen from C' group) - A low-grade alkylene (aryl which may have one or more substituents chosen from C' group), - low-grade alkylene CO- (aryl which may have one or more substituents chosen from C' group), and - either [low-grade alkyl and - low-grade ARUKENIRU or - low-grade alkynyl, however / at least] R1 or R2 - (low-grade alkyl which has one or more substituents chosen from B' group), - Or are - (low-grade alkynyl which has one or more substituents chosen from B' group), and (Low-grade ARUKENIRU which has one or more substituents chosen from B' group) [a;B' group] - ORa, -SRa, OH formed into - prodrug, the -O-low-grade alkylene RinD, -SORa, -SO2Ra, -SO2NRaRb, NRa-SO2Rb, -CO2H, - NRaRb, -NRc

- The low-grade alkylene RinD, -N(- low-grade alkylene RinD)2, -NRc
- The low-grade alkylene NRaRb, -N(low-grade alkylene NRaRb)2, - (5 which may have one or more substituents chosen from C' group, or 7 member saturation heterocycle), - (5 which may have one or more substituents chosen from C' group, or 6 member monocycle heteroaryl) - cycloalkyl, the -S-low-grade alkylene RinD, -NO

2, -CN, -CO2Ra, -CONRaRb, -NRa-CORb, Are OCORa and -CO-low-grade alkyl and -CO- (5 which may have one or more substituents chosen from C' group, or 6 member monocycle heteroaryl), and -;Ra, Rb and Rc are the same or different, are -H, - low-grade alkyl, or -RinD, and;RinD - (5 which may have one or more substituents chosen from C' group, or 7 member saturation heterocycle), - Or are - (5 which may have one or more substituents chosen from C' group, or 6 member monocycle heteroaryl), and (Aryl which may have one or more substituents chosen from C' group) [a;C' group] - Low-grade alkyl and - halogen, -ORa, -SRa, -NRaRb, - NO2, -CN, -CO2Ra, -CO-NRaRb, -CORa, - Are NRa-CORb and - OCO-Ra, and;R3 are -H or - low-grade alkyl, and [;A ring] - It is the condensation imidazolium inductor; and whose X- it is benzene ring which may have the substituent chosen from the group which consists of low-grade alkyl and -ORa, -NRaRb, -CN, a - halogen atom, and -NO2, and are counter anion.

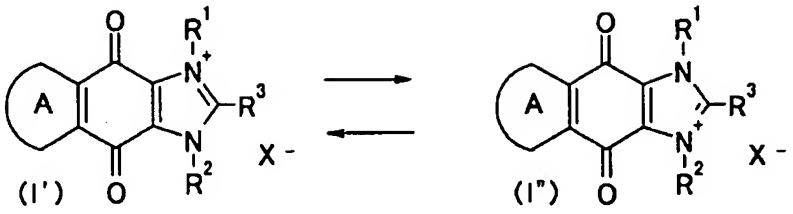
[0020]

[especially a desirable compound] among this invention compound (I) The 1-[(6-chloro 3-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, 1, the 2-dimethyl 4, 9-dioxo 3-[(2-tetrahydrofuranyl) methyl]-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, 1, the 3-bis(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 1-(2-pyrazinyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-[3-(1H-4-imidazolyl) propyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, 3-(2-methoxy ethyl)-2-methyl 1-[(5-methyl 2-pyrazinyl) methyl]-4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 2-methyl 4, 9-dioxo 1, 3-bis(2-pyrazinyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-[2-(2-methoxyethoxy) ethyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-{2-[2-(2-methoxyethoxy) ethoxy] ethyl}-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 3-(3-pyridyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 1-(2-pyridyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 1-(4-pyridyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-[(2-chloro 3-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-[(2-hydroxy 4-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 3-(2-methoxy ethyl)-1-[(6-methoxy 3-pyridyl) methyl]-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-[(2-chloro 4-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-(4-chloro benzyl)-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-(4-fluoro benzyl)-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, It is the salt of 1, 3-bis(2-methoxy ethyl)-2-methyl 5-nitroglycerine 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU or these tautomers, and a halogen ion.

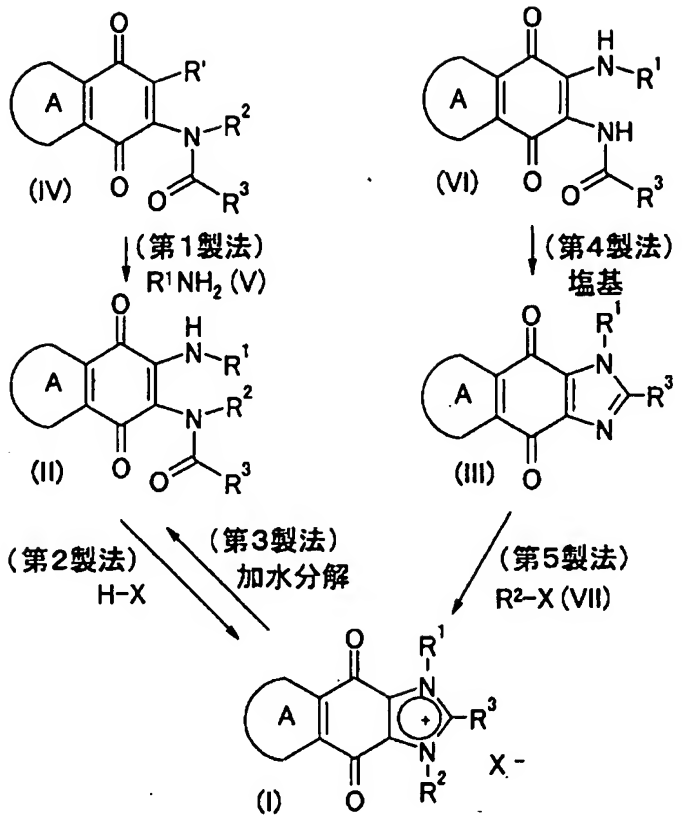
[0021]

The compound (I) of this invention has the tautomer shown by the bottom formula depended on delocalization of a cation, and the thing which these isomers separated, or a mixture is included by this invention. Therefore, the compound written as a 1H-imidazole 3-IUMU inductor includes the mixture of the 3H-imidazole 1-IUMU inductor which is a tautomer, and both isomers among this Description. In addition, when a compound (I) has substituent-COO- and forms imidazolium ion and inner salt, X- does

not exist.
[Formula 8]



[0022]
this invention compound (I) may form a salt depending on the kind of substituent in addition to a salt with said counter anion, and these salts are also included by this invention. Moreover, a salt may be formed depending on this invention compound (II) or (III) the kind of substituent, and these salts are also included by this invention. If it is the salt pharmaceutically permitted as a salt here, there will be no restriction in particular, but as acid addition salt Specifically Inorganic acids, such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid, formic acid, acetic acid, a propionic acid, an oxalic acid, malonic acid, succinic acid, a fumaric acid, a maleic acid, lactic acid, a malic acid, tartaric acid, citric acid, methansulfonic acid, ethane sulfonic acid, aspartic acid, It is mentioned by acid addition salt with organic acids, such as glutamic acid, etc., and as a salt with a base Salts, ammonium salt, etc. with an organic base, such as the inorganic base containing metals, such as sodium, potassium, magnesium, calcium, and an aluminium, or monomethylamine, ethylamine, ethanolamine, lysine, and ornithine, are mentioned.
Although a geometrical isomer and a tautomer may exist depending on the kind of this invention compound (I), (II), or (III) substituent, the thing which these isomers separated, or a mixture is included by this invention. Furthermore, this invention compound may have an asymmetric carbon atom, and the isomer based on an asymmetric carbon atom may exist. This invention includes the mixture and the thing which isolated of these optical isomers. Moreover, this invention compound may form N-oxide depending on the kind of substituent, and these N-oxide objects are also included by this invention. furthermore, this invention -- this invention compound (I) and (II) -- or (III) also includes the substance of various kinds of hydrates, solvate, and crystal polymorphism.
[0023]
(Manufacturing method)
A method this invention compound (I), (II), and (III) given in literature For example, J.Org.Chem. USSR, 1, and 1479-85 (1965), J. With the application of a well-known method, it can manufacture easily to a person skilled in the art, using the method indicated to Med.Chem., 7 (3), 362-364 (1964), JP, H3-258765,A, etc., and the same method.
In addition, depending on the kind of functional group, a raw material or a blocking group suitable in the stage of an intermediate product, i.e., transpose to the group which can be converted into the functional group concerned easily, may be effective on manufacture technology in the functional group concerned. The appropriate back can remove a blocking group if needed, and a desired compound can be obtained. As such a functional group, for example, an amino group, a hydroxyl group, Can mention a carboxyl group etc. and as those blocking groups The blocking group of ** (Greene), for example, Green, and the Wuts (Wuts) work, "Protective Groups in Organic Synthesis", and the 2nd-edition description can be mentioned, and what is necessary is just to use these suitably according to a reaction condition.
A typical production method is explained below.
[0024]
[Formula 9]



(Inside of formula and R' means hydrogen, methoxy or a halogen group, and the acids (preferably hydrogen fluoride, hydrogen chloride, a hydrogen bromide, hydrogen iodide, methansulfonic acid, ethane sulfonic acid, etc.) with which H-X forms anion.) the following -- the same .

[0025]

The 1st process

this invention compound (II) can be manufactured by making amines (V) react to a compound (IV) with a conventional method. A reaction, for example Chem.Pharm.Bull., 44 (6), 1181-1187 Syn.Comm., 27 (12), (1996) 2143-2157 Tetrahedron.Lett., 39 (42), (1997) 7677-7678 (1998) Etc. -- [it Can Manufacture with the application of the Method of Description, and] the compound (IV) of the inside of suitable inert solvents (for example, benzene etc.), and a reaction equivalent amount, and (V) -- again -- yes -- using inorganic bases (potassium carbonate etc.) or organic bases suitable as an acid supplement agent (triethylamine etc.) if needed using an excessive quantity of gaps or one side -- ordinary temperature or warming -- it is advantageous to carry out in the bottom.

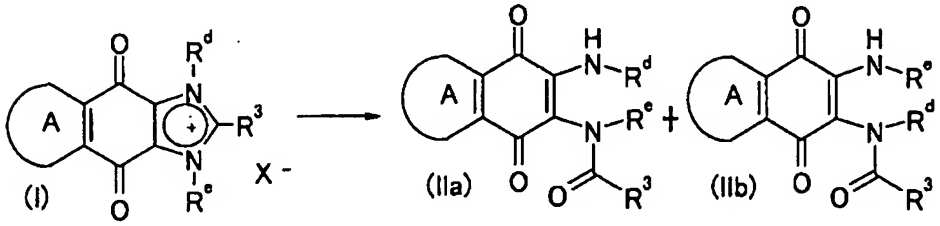
The 2nd process

With a conventional method, this invention compound (I) can manufacture this invention compound (II), cyclization and when the fourth class chlorinates. being able to perform a reaction with the application of the method of J.Org.Chem.USSR, 1, and given (1965) in 1479-85, for example, and using a reaction equivalent amount or an excessive quantity of acids among a suitable inert solvent (for example, alcoholic solvent) -- ordinary temperature or warming -- it is advantageous to carry out in the bottom.

[0026]

The 3rd process

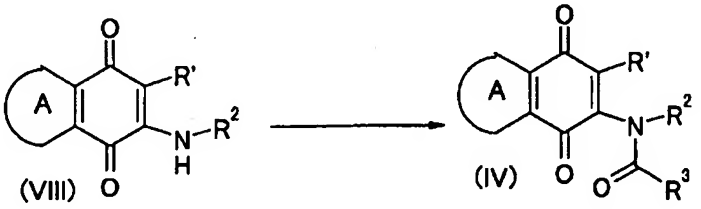
[Formula 10]



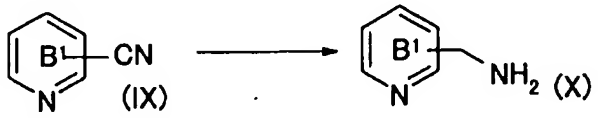
(Rd and Re show among a formula the arbitrary groups defined as R1 and R2.) the following -- the same .

hydrolyzing this invention compound (I) with a conventional method -- two sorts of this invention

compounds (IIa) -- and (IIb) it can obtain. The obtained compound can be further given to the modification reaction of a well-known group, and can also be made into the manufacture intermediate product of the desired this invention compound (I).
the hydrolysis reaction can apply the method of a description to J.Med.Chem., 7 (3), 362-364 (1964), etc., and a reaction equivalent amount or an excessive quantity of bases are used for it among water and a suitable inert solvent (for example, ethanol etc.), for example -- ordinary temperature or warming -- it is advantageous to carry out in the bottom. As a base, lithium hydroxide, sodium hydroxide, a potassium hydroxide, sodium carbonate, potassium carbonate, etc. are mentioned here.
[0027]
The 4th process
this invention compound (III) can be manufactured in accordance with the method indicated to J.Med. Chem., 39 (7), 1447-1451 (1996), etc. from giving a compound (VI) to ring closure under existence of bases, such as sodium hydroxide.
The 5th process
this invention compound (I) can be manufactured by making a halide (VII) react to this invention compound (III), and considering it as the fourth class salt. Reactions are J.Med.Chem., 7 (3), and 362-364, for example. Can carry out with the application of the method of a description (1964), and preferably the compound (III) of the inside of a suitable inert solvent (for example, alcoholic solvent), and a reaction equivalent amount -- and (VII) -- again -- yes -- using an excessive quantity of gaps or one side -- ordinary temperature or warming -- the bottom can carry out under the flowing-back temperature of a solvent preferably.
Other manufacturing methods
this invention compound can also be manufactured by the modification reaction of the well-known substituent of versatility besides the above-mentioned process. For example, the compound which has the substituent including sulfonyl combination can be manufactured by oxidation reaction of a conventional method from the compound which has a sulfide bond or sulfinyl combination. Moreover, N-oxide inductor of the compound which has heteroaryl containing N atoms, such as a pyridyl machine, as a substituent can be manufactured by oxidation reaction of a conventional method. The compound which has the substituent containing carboxylic acid can be manufactured by the hydrolysis reaction of a conventional method from the compound which has ester or amide combination. The compound which has the substituent containing an amino alkyl group can be manufactured by the amination reaction of a conventional method from the compound which has halogenation alkyl combination. When it is this invention compound (II) and (III) educt, it can be considered as a salt by the salt formation reaction according to a conventional method by request.
[0028]
Synthesis of a raw material compound
Some raw material compounds of this invention compound are new molecular entities, and these compounds can be easily compounded like a well-known raw material compound using a well-known method to a person skilled in the art. A typical synthetic process is shown below.
Synthetic process 1
[Formula 11]

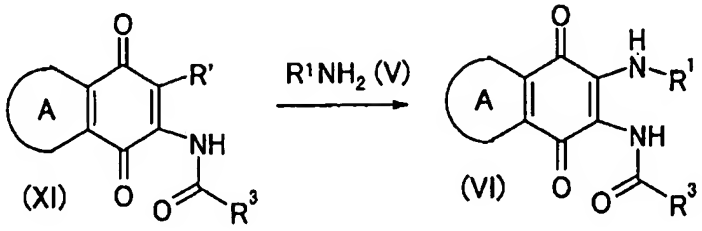


A compound (IV) meets the method indicated to J.Org.Chem.USSR, 1, 1479-85 (1965), etc., for example. A compound (VIII) can be manufactured by reactant carboxylic acid, such as acid halide and an acid anhydride, and the acylation reaction of a conventional method made to react.
Synthetic process 2
[Formula 12]

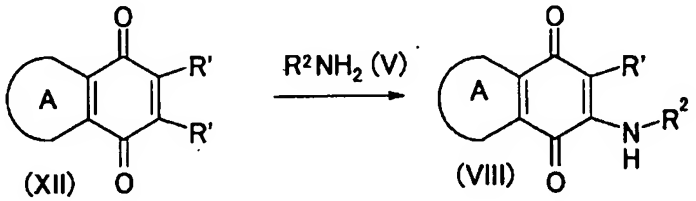


(B1 shows among a formula the pyridine ring which may have a substituent.) the following -- the same . an aminomethyl pyridine inductor (X) -- the German patent No. 3726993 gazette (1989) etc. -- in

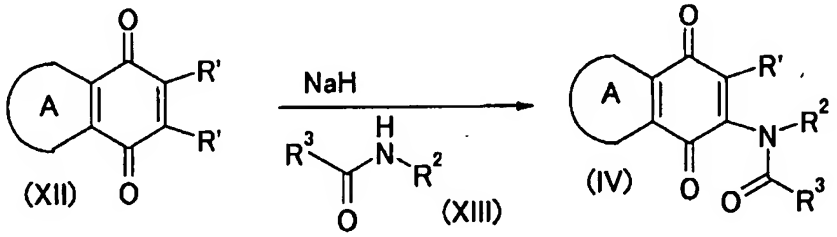
accordance with the indicated method, it can manufacture by reduction of a compound (IX).
[0029]
Synthetic process 3
[Formula 13]



A compound (VI) can be manufactured according to amination of a compound (XI) in accordance with the method indicated to J.Med.Chem., 39 (7), 1447-1451 (1996), etc.
Synthetic process 4
[Formula 14]



A compound (VIII) J.Het.Chem., 33 (1), 113-117 Syn.Comm., 27 (12), (1996) 2143-2157 (1997) In accordance with the method indicated to Tetrahedron.Lett., 39 (42), 7677-7678 (1998), etc., it can manufacture according to amination of a compound (XII).
[0030]
Synthetic process 5
[Formula 15]



A compound (IV) can be manufactured by amidation of a compound (XII). The inside of an inert solvent with an appropriate reaction (for example, N, N dimethylformamide (DMF) etc.), the reaction equivalent amount after activating the compound (XIII) of a reaction equivalent amount using suitable inorganic bases (NaH etc.) or organic bases (NaOMe etc.), an excessive quantity of compounds (XII) and ordinary temperature, or warming -- it is advantageous to make it react in the bottom.
Thus, isolation and refining of the manufactured this invention compound are performed by being adapted in the usual chemical operation, such as extraction, concentration, distilling off, crystallization, filtration, recrystallization, and various chromatography.
Various kinds of isomers can isolate with a conventional method using the difference of the physicochemical character between isomers. For example, racemate can be led to an isomer pure on the [method [for example,] of leading to diastereomeric salt with common optical activity acids (tartaric acid etc.), and carrying out optical resolution] solid target by a general optical resolution method. Moreover, the mixture of a diastereomer is separable with fractional-crystallization-izing or chromatography, for example. Moreover, an optical activity compound can also be manufactured by using a suitable optical activity raw material.
[0031]
[Effect of the Invention]
The compound (I) of this invention and (II) have good cancer cell multiplication depressant action, and, moreover, are useful as a large anticancer agent of a safety margin at low toxicity. therefore, this invention compound -- cancer -- desirable -- all the solid carcinota and a lymphoma -- it has the multiplication depressant action of tumors, such as skin carcinoma, vesical cancer, a breast cancer, a uterine cancer, an ovarian cancer, a prostatic cancer, lung cancer, colon cancer, a pancreatic cancer, a

renal cancer, and gastric cancer, especially, and is useful for these therapies. Especially, in a cancer cell growth inhibition examination and the in vivo cancer growth inhibition examination using a mouse cancer-bearing model, it has the good antitumor activity exceeding the existing anticancer agent to two or more cancer types, and is expected as a treating agent of the cancer type which shows the existing anticancer agent tolerance.

[0032]

The effect of this invention compound was checked by the following examinations.

Example 1 of an examination Cancer cell growth inhibition examination

(Test method) Cell culture: Uterine-cervix-carcinoma HeLaS3 cell or melanoma A375 cell was cultured by Dulbecco's modified eagle medium (GIBCO (DMEM)) which added FCS 10%.

Compound evaluation: In DMEM, seeding of HeLaS3 cell or the A375 cell was carried out to 96 hole plate for cultured cells (made by IWAKI), and it was cultured overnight. The last concentration of DMSO was made the same at 0.1%, the DMSO solution of the evaluation compound was added by various concentration, and the color reaction by Alamar Blue (Biosource) estimated the proliferation of cells 48 hours after addition on the next day.

(Result) The compound (I) of this invention and (II) checked multiplication of the cancer cell good, and the IC50 value was below 1microM.

[moreover, the compound (I) of this invention and (II)] other cancer cells (non-small cell lung cancer (EKVX, HOP-92, NCI-H358, A-549, NCI-H460) --) A breast cancer (MDA-MB-231, MCF7), a prostatic cancer (PC-3), It had good proliferation-of-cells prevention activity similarly to a pancreatic cancer (MIA PaCa-2), colon cancer (WiDr), a renal cancer (A-498), gastric cancer (MKN28), vesical cancer (UC-14), and fibrosarcoma (HT-1080).

[0033]

Example 2 of an examination in vivo cancer growth inhibition examination

(Test method) 2x106 of A375 cell strain which is a melanoma were transplanted to the back hypodermic of a male Balb/c nude mouse. The evaluation compound was administered intravenously once per two-week day from the time of tumor capacity reaching [three] in 50-100mm. Moreover, the physiological saline was administered intravenously to the control group. For measurement of the diameter of a tumor, it measured temporally till the next day of the last administration using slide calipers. Tumor capacity was computed in the following formulas.

Tumor capacity (mm3) = 1 / 2x [minor axis (mm)] 2x major axis (mm)

(Result) In the exam, this invention compound (I) and (II) controlled cancer multiplication good, for example, the compound of work examples 4, 37, 118, 121, 148, 154, 180, and 182 showed 50% or more of multiplication control activity to the control group in 0.3 or 1mg/kg of administration.

this invention compound showed good cancer multiplication depressant action similarly in the animal model which transplanted other cancer cells (a prostatic cancer (PC-3) or non-small cell lung cancer (NCI-H358, A-549, NCI-H460)).

[0034]

Example 3 of an examination Mouse single-dose toxicity study

(Test method) Single-dose administration of this invention compound was carried out to the Balb/C mouse by intravenous administration, and the existence of the example of death of a during [the observation period for two weeks] was examined.

(Result) In 3mg [/kg] single-dose administration, the example of death all did not have the compound of the work examples 4, 9, 35, 37, 52, 72, 121, 133, 148, 154, 158, 180, 182, 184, 185, 186, 192, and 197 of this invention. On the other hand in 3mg [/kg] single-dose administration, as for earlier literature Khim.Pharm.Zh., 32 (6), KP-1 that were indicated by 10-11 (1998), and KP-3, the example of all [in two examples] died, respectively. Therefore, it was shown that this invention compound has low toxicity as compared with an earlier literature compound.

Therefore, it was shown that it is useful as a treating agent of cancer which this invention compound (I) and (II) have good antitumor activity to two or more cancer types, and has a good profile from moreover it being low toxicity.

[0035]

The medicine constituent of this invention can be prepared by one sort of the compound shown by a general formula (I) or (II) or two sorts or more, and the method usually used using the carriers (the carrier for drugs, an excipient, etc.) which are usually used in the field for the time being, and which are permitted pharmaceutically. Administration may be which form of the parenteral administration by injections, such as internal use by a tablet, a pill, a capsule, the granule, powder, liquid medicine, inhalations, etc. or intravenous injection, and intramuscular injection, suppositories, ophthalmic solutions, an ophthalmic ointment, the liquid medicine for transderma, an ointment, the patches for transderma, permucosal liquid medicine, permucosal patches, etc.

A tablet, powder, a granule, etc. are used as a solid constituent for internal use by this invention. In such a solid constituent **, one, or the active substance beyond it is mixed with at least one inactivity

excipient, for example, milk sugar, a mannitol, grape sugar, hydroxypropylcellulose, a microcrystal cellulose, a starch, a polyvinylpyrrolidone, magnesium aluminometasilicate, etc. The constituent may contain disintegrator, such as lubricant, such as an inactivity additive agent, for example, magnesium stearate etc., and carboxy-methyl-starch sodium, and a solubilizing agent according to a conventional method. You may carry out the film of a tablet or the pill by sugar-coating, stomach solubility, or an enteric coating agent as occasion demands.
The liquid constituent for internal use contains the inactivity solvent generally used, for example, purified water, and ethanol including an emulsion, liquid medicine, suspension, syrups, elixirs, etc. which are permitted in drugs. This constituent may contain a solubilizer, a wetting agent, an auxiliary material like a suspending agent, a sweetening agent, corrigent, the aromatic, and the preservative in addition to an inactivity solvent.
[0036]
As injections for parenteral administration, sterile water or non-aqueous liquid medicine, suspension, and an emulsion are contained. As a water solvent, distilled water for injection and a physiological saline are contained, for example. As a non-aqueous solvent, there are propylene glycol, a polyethylene glycol, vegetable oil like olive oil, alcohols like ethanol, polysorbate 80 (brand name), etc., for example. Such a constituent may also contain an isotonizing agent, a preservative, a wetting agent, an emulsifier, a dispersing agent, a stabilizing agent, and a solubilizing agent further. These are sanitized by the combination or radiation of filtration and a fungicide which lets for example, a bacteria suspension filter pass. Moreover, these manufacture a sterile solid constituent, and they can also use it for non-bacterial water or the sterile solvent for injection before use, dissolving and suspending it in it.
Usually, when 50mg/kg of doses on the 1st are preferably administered intravenously in 0.01-30mg/kg from about 0.001 in internal use, the dose on the 1st is 10mg/kg from about 0.0001,
Preferably, kg is suitable respectively in 3mg /from about 0.001, and this is prescribed for the patient in 1 time per or two or more steps day. A dose is suitably determined according to each case in consideration of condition, age, sex, etc.
[0037]
[Example]
Based on a work example, this invention is explained still in detail hereafter. this invention compound is not limited to a compound given in the following work example at all. In addition, the example of manufacture of the raw material compound of this invention compound is shown in the example of reference.
Example 1 of reference: Saturated ammonia water (17ml) and Raney nickel (3.0g) were added to the ethanol (50ml) solution of the 3-cyano 2-(dimethylamino) pyridine (2.45g), and it agitated at the room temperature under the hydrogen atmosphere of breath pressure for 8 hours. The catalyst was ****(ed) after 760ml of hydrogen absorption. Mother liquor was condensed and the yellow oil-like 3-(aminomethyl)-2-(dimethylamino) pyridine (2.61g) was obtained.
Example 2 of reference: Several drops of strong sulfuric acid was added to the acetic anhydride (100ml) solution of 2-chloro 3-[(2-methoxy ethyl) amino]-1 and 4-naphtoquinone (33g), and it agitated at 45 degrees C for 1 hour. Ethanol (100ml) was added to reaction mixture, and the superfluous acetic anhydride was esterificated. Ethyl acetate was added after radiationnal cooling and it dried with anhydrous sodium sulfate after washing with water and saturation saline solution. The solvent was distilled off, the residue was crystallized from diethylether and N-(3-chloro 1, 4-dihydro1, 4-dioxo 2-naphtha RENIRU)-N-(2-methoxy ethyl) acetamido (29g) of yellow powder was obtained.
[0038]
Example 3 of reference: 2-methoxy ethylamine (0.8ml) was added to the benzene (20ml) solution of N-(3-chloro 1, 4-dihydro1, 4-dioxo 2-naphtha RENIRU) acetamido (1.0g), and it agitated under the room temperature for 1 hour. Water was added to reaction mixture and chloroform extracted. The organic layer was dried with anhydrous sodium sulfate after washing with water and saturation saline solution. The solvent was distilled off, recrystallization of the residue was carried out from ethyl acetate, and N-[3-(2-methoxy ethyl) amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU] acetamido (0.87g) of red powder was obtained.
Example 4 of reference: 2-(aminomethyl) pyrazine (3.2g) and diisopropyl ethylamine (5.8ml) were added to the benzene (90ml) solution of 2, 3-dichloro 1, 4-dihydro1, and 4-dioxo naphthalene (3.0g), and it agitated under the room temperature for 8 hours. The solid which added water to reaction mixture and deposited was ****(ed), and ethyl acetate extracted filtrate. The organic layer was dried with anhydrous sodium sulfate after washing with water and saturation saline solution. Silica gel column chromatography (eluted under chloroform) refined the residue after distilling off a solvent, and 2-chloro [of brown powder] 1, 4-dihydro1, and 4-dioxo 3-[(2-pyrazinyl methyl) amino] naphthalene (0.23g) was obtained.
[0039]
Example 5 of reference: Chlorination 2-chloro acetyl (3.3ml) was added to 1 of 2-chloro 1, 4-dihydro3-

methylamino 1, and 4-dioxo naphthalene (2.2g), and 4-dioxane (30ml) solution, and it agitated under flowing back for 14 hours. The solvent was distilled off after cooling reaction mixture radiationally. The solid which added ethanol to the residue and deposited was ****(ed). The obtained solid was recrystallized from ethanol and 2-chloro N-(3-chloro 1, 4-dihydro1, 4-dioxo 2-naphtha RENIRU)-N-methyl acetamido (2.6g) of yellow powder was obtained.

Example 6 of reference: NaH (440mg) was added to the DMF (20ml) solution of the 2-oxo-piperidine (1.0g), and it agitated for 30 minutes at the room temperature. This solution was added to the DMF (150ml) solution of 2, 3-dichloro 1, 4-dihydro1, and 4-dioxo naphthalene (6.9g) at a stretch, and it agitated at the room temperature for 17 hours. Reaction mixture was opened in saturated ammonia water, the depositing solid was ****(ed), and ethyl acetate extracted filtrate. The organic layer was dried with anhydrous sodium sulfate after washing with water and saturation saline solution. Silica gel column chromatography (eluted with ethyl acetate hexane 1:10 solution) refined the residue after distilling off a solvent, and 2-chloro [of brown powder] 1, 4-dihydro1, and 4-dioxo 3-(2-oxo-piperidino) naphthalene (0.49g) was obtained.

[0040]

Example 7 of reference: 2-methoxy ethylamine (1.6ml) was added to the tetrahydrofuran (100ml) solution of 4, 7-dihydro4, and 7-dioxo [benzob] thiophene 2-carboxylic acid methyl (2.4g), and it agitated at the room temperature for 27 hours. Silica gel column chromatography (eluted under chloroform) refined the residue after distilling off a solvent, and 4 of yellow powder, the 7-dihydro5-(2-methoxy ethyl) amino 4, and 7-dioxo [benzob] thiophene 2-carboxylic acid methyl (1.5g) were obtained.

Example 8 of reference: Five drops of strong sulfuric acid was added to the acetic anhydride (20ml) solution of 4, the 7-dihydro5-(2-methoxy ethyl) amino 4, and 7-dioxo [benzob] thiophene 2-carboxylic acid methyl (1.2g), and it agitated at the room temperature for 1 hour. The solvent was distilled off after adding methanol (20ml) to reaction mixture gradually. Water was added to the residue and ethyl acetate extracted. The organic layer was dried with anhydrous sodium sulfate after washing with water and saturation saline solution. Solvent Silica gel column chromatography (eluted with ethyl acetate hexane 1:1 solution) refines a residue after distilling off. Dark reddish-brown oil-like 5-[N-acetyl N-(2-methoxy ethyl) amino]-4, 7-dihydro4, and 7-dioxo [benzob] thiophene 2-carboxylic acid methyl (0.39g) was obtained.

The compound of the example 16 of reference which shows the compound of the examples 13-15 of reference which show the compound of the example 12 of reference which shows the compound of the examples 9-11 of reference shown in Table 3 in Table 4 like the example 2 of reference like the example 1 of reference in Table 4 like the example 3 of reference in Table 4 like the example 5 of reference was obtained, respectively.

[0041]

Work example 1: 2M sodium hydroxide aqueous solution (0.9ml) was added to the ethanol (10ml) solution of N-[3-(2-methoxy ethyl) amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU] acetamido (0.5g), and it agitated for 15 minutes under the room temperature. Water was added to reaction mixture and ethyl acetate extracted. The organic layer was dried with anhydrous sodium sulfate after washing with water and saturation saline solution. The solvent was distilled off, the residue was washed in **** and ethanol, and 1-(2-methoxy ethyl)-2-methyl [of light orange powder] 4, 9-dihydro4, and 9-dioxo 1H-[2 and 3-naphth d] imidazole (0.58g) was obtained.

Work example 2: Benzylamine (0.5ml) was added to the benzene (15ml) solution of N-(3-chloro 1, 4-dihydro1, 4-dioxo 2-naphtha RENIRU)-N-(2-methoxy ethyl) acetamido (0.5g), and it agitated at the room temperature for 4 hours. Ethyl acetate was added to reaction mixture and it dried with sulphuric anhydride magnesium after washing with water and saturation saline solution. The solvent was distilled off, the residue was crystallized from ethyl acetate hexane, and N-(3-benzylamino 1, 4-dihydro1, 4-dioxo 2-naphtha RENIRU)-N-(2-methoxy ethyl) acetamido (0.51g) of red powder was obtained.

[0042]

Work example 3: It is 3-chloro perbenzoic acid (0.6g) 80% to the dichloromethane (20ml) solution of N-(2-methoxy ethyl)-N-[3-(3-pyridyl methyl) amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU] acetamido (0.95g). In addition, it agitated at the room temperature for 18 hours. The saturation sodium bicarbonate aqueous solution was added to reaction mixture, and it extracted in dichloromethane. The organic layer was dried with anhydrous sodium sulfate after washing with water and saturation saline solution. Solvent Distill off and silica gel column chromatography (eluted with 10:1:0.chloroform methanol saturated ammonia water 1 solution) refines a residue. 3-[({3-[N-acetyl N-(2-methoxy ethyl)] amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU} amino) methyl] pyridine of a brown amorphous-like solid 1-oxide (0.84g) was obtained.

Work example 4: [the ethanol (30ml) solution of chlorination 1-(2-methoxy ethyl)-2-methyl 3-(4-pyridyl methyl)-4, 9-dihydro4, and 9-dioxo 1H-[2 and 3-naphth d] imidazole 3-IUMU a little salt acid chloride (1.1g)] 1M sodium hydroxide aqueous solution (5.0ml) In addition, it agitated for 30 minutes at the room temperature. Water was added to reaction mixture and ethyl acetate extracted. The organic

layer was dried with sulphuric anhydride magnesium after washing with water and saturation saline solution. The solvent was distilled off and silica gel column chromatography (fraction A: eluted in elution and fraction B:ethyl acetate with ethyl acetate hexane 1:1 solution) refined the residue. Fraction A was crystallized from diethylether and N-[3-(2-methoxy ethyl) amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU]-N-(4-pyridyl methyl) acetamido (0.2g) of red powder was obtained. In addition, it is although Fraction B was crystallized from ethyl acetate and yellow powder (0.31g) was obtained, This was the same compound as N-(2-methoxy ethyl)-N-[3-(4-pyridyl methyl) amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU] acetamido of after-mentioned work-example 37 description.

[0043]

Work example 5: It is 3-chloro perbenzoic acid (0.78g) 80% to the dichloromethane (10ml) solution of N-methyl N-{3-[2-(methyl sulfinyl) ethyl] amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU} acetamido (0.52g). In addition, it agitated at the room temperature for 3 hours. The saturation sodium bicarbonate aqueous solution was added to reaction mixture, and it extracted in dichloromethane. The organic layer was dried with anhydrous sodium sulfate after washing with water and saturation saline solution. Solvent Distill off and silica gel column chromatography (eluted with chloroform methanol 50:1 solution) refines a residue. N-methyl N-{3-[2-(methylsulfonyl) ethyl] amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU} acetamido (0.39g) of the orange amorphous-like solid was obtained.

Work example 6: N-[3-(2-hydroxyethyl) amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU]-N-methyl acetamido (0.4g) After carrying out a suspension to ethanol (3ml), 4M hydrogen chloride / ethyl acetate solution (3ml) was added, and it agitated at 45 degrees C for 1 hour. **** and ethyl acetate washed the produced precipitation after radiationnal cooling. The obtained solid was recrystallized from ethanol ethyl acetate, and chlorination 1-(2-hydroxyethyl)-2 in end of non-color powder, 3-dimethyl 4, 9-dihydro4, and 9-dioxo 1H-[2 and 3-naphth d] imidazole 3-IUMU (0.28g) was obtained.

Work example 7: The benzyl bromide (1.9ml) was added to the acetonitrile (20ml) solution of 1-isopropyl 2-methyl 4, 9-dihydro4, and 9-dioxo 1H-[2 and 3-naphth d] imidazole (0.8g), and it agitated under flowing back for 6 hours. **** and ethyl acetate washed the produced precipitation after radiationnal cooling. The obtained solid was recrystallized from methanol and bromination 1-benzyl 3-isopropyl 2-methyl [of yellow powder] 4, 9-dihydro4, and 9-dioxo 1H-[2 and 3-naphth d] imidazole 3-IUMU (0.47g) was obtained.

work example 8: the same method as a work example 6 -- N-(2-methoxy ethyl)- [acetamido / (0.49g) / N-{3-[(2-methoxy 3-pyridyl) methyl] amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU}] The chlorination 1-(2-hydroxy 3-pyridyl) methyl 3-(2-methoxy ethyl)-2-methyl 4 of brown powder, 9-dihydro4, and 9-dioxo 1H-[2 and 3-naphth d] imidazole 3-IUMU (0.39g) It obtained.

[0044]

Work example 9: They are 4M hydrogen chloride / ethyl acetate solution (10ml) to the ethanol (10ml) solution of N-{3-[(6-chloro 3-pyridyl) methyl] amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU}-N-(2-methoxy ethyl) acetamido (0.8g). In addition, it agitated for one day at the room temperature. Solvent **** and ethyl acetate wash a residue after distilling off. The chlorination 1-[(6-chloro 3-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4 of thin yellow powder, 9-dioxo 4, and 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU (0.82g) were obtained.

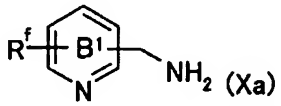
work example 10: They are 2M dimethyl amine / tetrahydrofuran solution (3.0ml) to the tetrahydrofuran (30ml) solution of 2-chloro N-[1, 4-dihydro3-(2-methoxy ethyl) amino 1, and 4-dioxo 2-naphtha RENIRU]-N-methyl acetamido (0.5g). In addition, it agitated at the room temperature for 18 hours. Water was added to reaction mixture and ethyl acetate extracted. The organic layer was dried with sulphuric anhydride magnesium after washing with water and saturation saline solution. The residue was crystallized from ethanol after distilling off a solvent, and N-[1, 4-dihydro3-(2-methoxy ethyl) amino 1, and 4-dioxo 2-naphtha RENIRU]-N-methyl 2-(dimethylamino) acetamido (0.19g) of brown powder was obtained.

Work example 11: It is 2-methoxy ethylamine (0.15ml) to the tetrahydrofuran (30ml) solution of 5-[N-acetyl N-(2-methoxy ethyl) amino]-4, 7-dihydro4, and 7-dioxo [benzob] thiophene 2-carboxylic acid methyl (0.39g). In addition, it agitated at the room temperature for 6.5 hours. Solvent Silica gel column chromatography (eluted with hexane ethyl acetate 50:1 solution) refines a residue after distilling off. Purplish red color oil-like 4 [5-[N-acetyl N-(2-methoxy ethyl) amino]-], the 7-dihydro6-(2-methoxy ethyl) amino 4, and 7-dioxo [benzob] thiophene 2-carboxylic acid methyl (0.39g) were obtained.

Work example 12: They are 4M hydrogen chloride / ethyl acetate solution (2.5ml) to the methanol (30ml) suspension of 3-{[4[the 3-(N-acetyl N-methyl) amino 1, 4-dihydro1, and]-dioxo 2-naphtha RENIRU] Amino} pro PIONAMIDO (0.32g). In addition, it agitated at the room temperature for 16 hours. The solvent was distilled off after radiationnal cooling and heating churning of the residue was carried out in ethanol. The produced precipitation was washed by **** and ethanol after radiationnal cooling, and chlorination 1-(2-carboxyethyl)-4 in end of non-color powder, 9-dihydro2, 3-dimethyl 4, and 9-dioxo 1H-[2 and 3-naphth d] imidazole 3-IUMU (0.15g) was obtained.

The work-example compound of the description was obtained to the after-mentioned tables 6-20 like the

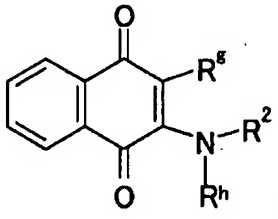
above-mentioned work examples 1-9.
The constitutional formula and physicochemical character of a work-example compound are shown in the after-mentioned tables 3-5 in Tables 6-20 at the row of the example compound of reference, respectively. Moreover, almost like a method given in said work example or a manufacturing method, the compound [thing mentioned above / Tables 21-27 / a compound / a chemical structure type] applies some obvious strange method to a person skilled in the art at them, or is manufactured easily.
[0045]
cable address [ ] in front -- Sy:manufacturing method Example of Ref:reference; Ex: -- work example; Co:compound number; Sal: -- salt; ([a number / the number of said work example / show and]) It is the same method as said this work example about the compound concerned. [having manufactured] it is shown -- Dat:physicochemical character; Do not do -:existence of.; (F:FAB-MS (M)+; F':FAB-MS (M)-; F+:FAB-MS+(M+H); F-:FAB-MS-(M-H); E:EI-MS(M)+;) characteristic peak deltappm of N1:1 H-NMR (DMSO-d6, TMS internal standard); i-Pr: -- isopropyl; c-Pr:cyclo propyl; Ad:1-adamanthyl; Ac: -- acetyl; Bn: -- benzyl; Pipe; -- piperidino; Morp; -- morpholino; Py2;2-pyridyl; Py3;3-pyridyl; Py4;4-pyridyl; Th;2-thienyl; Fu;2-furil; Thf;2-tetrahydrofuranyl; Pyr;2-pyrazinyl; 5-MePyr;5-methyl 2-pyrazinyl; Pym;4-pyrimidinyl; Qu;3-quinolyl; Dio;4-benzodioxolyl; Im;4-imidazolyl; Bim;2-benzoimidazolyl; -- and -- In;2-India Lil is shown, respectively. In addition, the number in front of a substituent shows a substitution position, for example, is 3 and 4-Cl.
: It is shown that -Cl replaces by the 3rd place and the 4th place, respectively.
[0046]
[Table 3]



(Xa)

Ref	B^1	$-R^f$	Dat	Ref	B^1	$-R^f$	Dat
1	Py3	2-NMe_2	F+: 152	10	Py4	2-NMe_2	F+: 152
9	Py3	6-NMe_2	F+: 152	11	Py3	2-OMe	E: 138

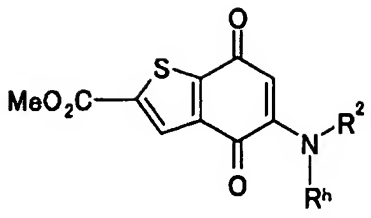
[0047]
[Table 4]



(IVa) or (VIa) or (VIIIa)

Ref	$-R^g$	$-R^h$	R^2	Dat
2	-Cl	-Ac	$-(CH_2)_2OMe$	N1: 1.88(3H,s), 2.99(3H,s), 3.3-3.9(4H,m), 7.9-8.2(4H,m)
3	$-NH-(CH_2)_2OMe$	-Ac	-H	F+: 289
4	-Cl	-H	$-CH_2Pyr$	F': 299
5	-Cl	$-COCH_2Cl$	-Me	F: 298
6	-Cl	$-CO(CH_2)_4-$		F+: 290
12	-Cl	-Ac	$-CH_2Pyr$	F': 341
13	$-NH-CH_2$(Py3)	-Ac	-H	F+: 322
14	$-NH-CH_2$(Py4)	-Ac	-H	F+: 322
15	$-NH-CH_2$(Pyr)	-Ac	-H	F+: 323
16	-Cl	$-COCH_2OMe$	-Me	F+: 294

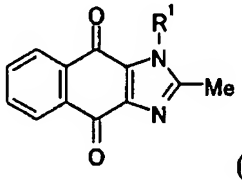
[0048]
[Table 5]



(IVb) or (VIIIb)

Ref	R^h	R^2	Dat
7	-H	$-(CH_2)_2OMe$	F+: 296
8	-Ac	$-(CH_2)_2OMe$	F+: 338

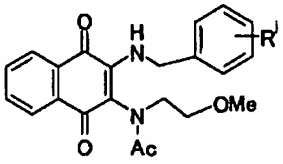
[0049]
[Table 6]



(IIIa)

Ex.	$-R^1$	Dat	Ex.	$-R^1$	Dat
1	$-(CH_2)_2OMe$	F+: 271	14	$-CH_2$(Py4)	F+: 304
13	$-CH_2$(Py3)	F+: 304	15	$-CH_2$(Pyr)	F+: 305

[0050]
[Table 7]

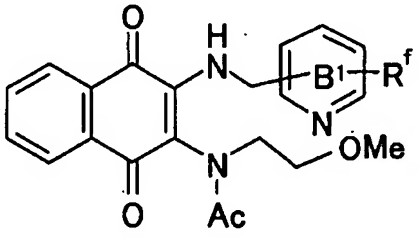


(IIc)

Ex	$-R^j$	Sy	Dat
2	-H	-	F+: 379 N1: 1.34(3H,br), 3.06(3H,s), 3.1-3.8(4H,m), 4.5-4.8(2H,m), 7.2-7.4(5H,m), 7.77(1H,dt), 7.85(1H,dt), 7.93(1H,br), 7.98(1H,d), 8.03(1H,d)
16	2-Cl	2	F+: 413
17	3-Cl	2	F+: 413
18	4-Cl	2	F+: 413 N1: 1.39(3H,br), 3.06(3H,s), 3.1-3.4(2H,m), 3.4-3.5(1H,m), 3.6-3.9(1H,m), 4.5-4.8(2H,m), 7.27(2H,d), 7.38(2H,d), 7.7-8.1(4H,m)
19	3,4-Cl	2	F: 447
20	2-OMe	2	F+: 409
21	3-OMe	2	F+: 409
22	4-OMe	2	F+: 409
23	4-Ph	2	F+: 455
24	2-CN	2	F+: 404
25	3-CN	2	F+: 404
26	4-CN	2	F+: 404
27	$4-SO_2NH_2$	2	F+: 458
28	$4-CF_3$	2	F+: 447
29	4-F	2	F+: 397 N1: 1.40(3H,br), 3.06(3H,s), 3.1-3.6(3H,m), 3.79(1H,br), 4.5-4.8(2H,m), 7.1-7.2(2H,m), 7.2-7.5(2H,m), 7.7-8.2(4H,m)
30	4-Br	2	F+: 457, 459
31	$3-CH_2NH_2$	2	F+: 408

31	3-CH_2NH_2	2	F+: 408
32	4-CH_2NH_2	2	F: 407
33	3-NO_2	2	F+: 424
34	4-NO_2	2	F+: 424 N1: 1.39(3H,br), 3.07(3H,s), 3.1-3.6(3H,m), 3.6-3.9(1H,m), 4.6-5.0(2H,m), 7.54(2H,d), 7.7-8.2(5H,m), 8.19(2H,d)

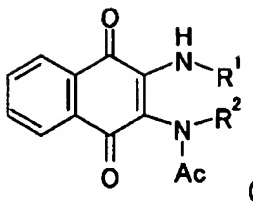
[0051]
[Table 8]



(IId)

Ex	B^1	-R^f	Sy	Dat
3	Py3	1-oxide	-	F+: 396
35	Py3	-H	2	F+: 380 N1: 1.40(3H,s), 3.06(3H,s), 3.1-3.8(4H,m), 4.6-4.8(2H,m), 7.34(1H,dd), 7.6-8.1(6H,m), 8.4-8.5(2H,m)
36	Py2	-H	2	F+: 380 N1: 1.62(3H,s), 3.06(3H,s), 3.2-3.9(4H,m), 4.5-5.0(4H,m), 7.2-7.5(2H,m), 7.7-8.2(6H,m), 8.54(1H,d)
37	Py4	-H	2	F+: 380 N1: 1.38(1H,br), 3.07(3H,s), 3.1-3.8(4H,m), 4.6-4.8(2H,m), 7.26(2H,d), 7.77(1H,dt), 7.85(1H,dt), 7.95(1H,d), 8.01(1H,d), 8.48(2H,d)
38	Py3	2-Cl	2	F+: 414 N1: 1.49(3H,s), 3.07(3H,s), 3.1-3.4(2H,m), 3.4-3.6(1H,m), 3.6-3.8(1H,m), 4.6-4.9(2H,m), 7.3-7.5(1H,m), 7.7-8.2(6H,m)
39	Py3	6-Cl	2	F+: 414 N1: 1.47(3H,br), 3.07(3H,s), 3.1-3.6(3H,m), 3.6-4.0(1H,m), 4.6-4.9(2H,m), 7.48(1H,d), 7.6-8.1(6H,m), 8.34(1H,d)
40	Py3	2-OMe	2	F+: 410
41	Py3	6-OMe	2	F+: 410 N1: 1.49(3H,s), 3.07(3H,s), 3.1-3.5(3H,m), 3.6-3.9(4H,m), 4.5-4.8(2H,m), 6.79(1H,d), 7.5-7.7(1H,m), 7.7-8.2(5H,m)
42	Py3	2-NMe_2	2	F+: 423
43	Py3	6-NMe_2	2	F+: 423
44	Py3	5-Me	2	F+: 394
45	Py3	6-Me	2	F: 393
46	Py3	6-CF_3	2	F+: 448
47	Py4	2-Cl	2	F+: 414 N1: 1.48(3H,br), 3.09(3H,s), 3.1-3.6(3H,m), 3.6-3.9(1H,m), 4.5-5.0(2H,m), 7.33(1H,d), 7.45(1H,s), 7.6-8.2(5H,m), 8.34(1H,d)
48	Py4	2-NMe_2	2	F+: 423
49	Py4	2-OMe	2	F+: 410

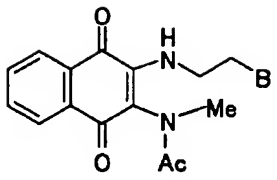
[0052]
[Table 9]



(IIe)

Ex	-R^1	-R^2	Sy	Dat
4	-$(CH_2)_2OMe$	-CH_2(Py4)	-	F+: 380 N1: 1.19(3H,s), 3.26(3H,s), 3.47(4H,br), 4.27(1H,d), 4.81(1H,d), 7.10(1H,br), 7.35(2H,d), 7.74(1H,dt), 7.82(1H,dt), 7.92(1H,d), 7.98(1H,d), 8.41(2H,d)
50	-$(CH_2)_2OMe$	-$(CH_2)_2OMe$	2	N1: 1.83(3H,s), 3.0-3.8(14H,m), 6.9-7.1(1H,m), 7.7-7.9(2H,m), 7.9-8.1(2H,m)
51	-$(CH_2)_2OMe$	-Bn	2	N1: 1.88(3H,s), 3.23(3H,s), 3.3-3.5(4H,m), 4.4-4.7(2H,m), 6.91(1H,br), 7.1-7.4(5H,m), 7.6-8.1(4H,m)
52	-$(CH_2)_2OMe$	-CH_2(Py3)	4	F+: 380 N1: 1.87(3H,s), 3.25(3H,s), 3.4-3.6(4H,m), 4.31(1H,d), 4.81(1H,d), 7.08(1H,br), 7.23(1H,dd), 7.6-7.8(2H,m), 7.81(1H,t), 7.88(1H,d), 7.98(1H,d), 8.37(1H,d), 8.45(1H,s)
53	-Bn	-Bn	2	F+: 411
54	-CH_2(Py4)	-Bn	2	F+: 412
55	-CH_2(Py3)	-Bn	2	F+: 412
56	-$(CH_2)_2Ph$	-$(CH_2)_2OMe$	2	F+: 393
57	-CH_2Th	-$(CH_2)_2OMe$	2	F+: 387
58	-CH_2Fu	-$(CH_2)_2OMe$	2	F+: 369
59	-CH_2Pyr	-$(CH_2)_2OMe$	2	F+: 381 N1: 1.60(3H,s), 3.07(3H,s), 3.2-3.8(4H,m), 4.5-5.3(2H,m), 7.5-8.2(5H,m), 8.5-8.8(3H,m)
60	-CH_2Qu	-$(CH_2)_2OMe$	2	F+: 430
61	-$(CH_2)_2$(Py2)	-$(CH_2)_2OMe$	2	F+: 394
62	-$(CH_2)_2$(Py3)	-$(CH_2)_2OMe$	2	E: 393
63	-$(CH_2)_2$(Py4)	-$(CH_2)_2OMe$	2	F+: 394
64	-$(CH_2)_2In$	-$(CH_2)_2OMe$	2	F+: 432
65	-CH_2Dio	-$(CH_2)_2OMe$	2	F+: 423
66	-$(CH_2)_3Im$	-$(CH_2)_2OMe$	2	F+: 397
67	-$(CH_2)_2Im$	-$(CH_2)_2OMe$	2	F+: 383
68	-CH_2Bim	-$(CH_2)_2OMe$	2	F+: 419
69	-$(CH_2)_2O(CH_2)_2NH_2$	-$(CH_2)_2OMe$	2	F+: 376
70	-$(CH_2)_5NH_2$	-$(CH_2)_2OMe$	2	F+: 374
71	-$(CH_2)_2O(CH_2)_2$- $O(CH_2)_2NH_2$	-$(CH_2)_2OMe$	2	F+: 420

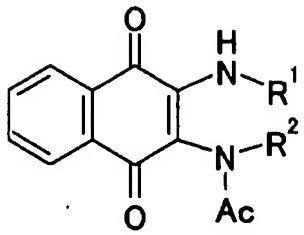
[0053]
[Table 10]



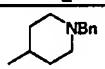
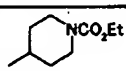
(IIf)

Ex	-B	Sy	Dat
5	$-SO_2Me$	-	F+: 351
72	-OMe	2	F+: 303 N1: 1.83(3H,s), 2.92(3H,s), 3.29(3H,s), 3.4-3.7(4H,m), 7.11(1H,br), 7.7-7.9(2H,m), 7.9-8.1(2H,m)
73	-OPh	2	N1: 1.83(3H,s), 2.93(3H,s), 3.6-3.9(2H,m), 4.21(2H,t), 6.8-7.1(3H,m), 7.2-7.5(3H,m), 7.7-7.9(2H,m), 7.9-8.1(2H,m)
74	-OBn	2	N1: 2.89(3H,s), 3.90(2H,t), 4.19(3H,s), 4.45(2H,s), 4.89(2H,t), 7.1-7.5(5H,m), 7.9-8.1(2H,m), 8.1-8.3(2H,m)
75	$-NMe_2$	2	F+: 316 N1: 1.83(3H,s), 2.18(6H,s), 2.4-2.6(2H,m), 2.94(3H,s), 3.2-3.5(2H,m), 7.14(1H,t), 7.7-7.9(2H,m), 7.9-8.1(2H,m)
76	-OEt	2	F+: 317 N1: 1.10(3H,t), 1.82(3H,s), 2.92(3H,s), 3.3-3.7(6H,m), 7.09(1H,br), 7.7-7.9(2H,m), 7.9-8.1(2H,m)
77	-OPr	2	F+: 331 N1: 0.85(3H,t), 1.4-1.6(2H,m), 1.83(3H,s), 2.92(3H,s), 3.37(2H,t), 3.4-3.7(4H,m), 7.08(1H,br), 7.7-7.9(2H,m), 7.9-8.1(2H,m)
78	-O(i-Pr)	2	F+: 331 N1: 1.07(6H,d), 1.82(3H,s), 2.92(3H,s), 3.4-3.7(5H,m), 7.08(1H,br), 7.7-7.9(2H,m), 7.9-8.1(2H,m)
79	$-O(CH_2)_2NH_2$	2	F+: 332
80	$-OCH_2$(Py3)	2	F+: 413 N1: 1.79(3H,s), 2.90(3H,s), 3.5-3.8(4H,m), 4.55(2H,s), 7.1-7.3(1H,m), 7.2-7.5(1H,m), 7.7-7.9(3H,m), 7.9-8.1(2H,m), 8.4-8.6(2H,m)
81	-SMe	2	F+: 319
82	$-NEt_2$	2	F+: 344
83	$-N(i\text{-}Pr)_2$	2	F+: 372
84	-Pipe	2	F+: 356
85	-Morp	2	F+: 358
86	-NHAc	2	F+: 330 N1: 1.81(6H,s), 2.90(3H,s), 3.2-3.7(4H,m), 7.36(1H,br), 7.7-8.2(5H,m)
87	-OCONHPh	2	F+: 408
88	$-CONH_2$	2	F+: 316
89	-CN	2	F+: 298
90	$-O(CH_2)_2OMe$	2	F+: 347

[0054]
[Table 11]



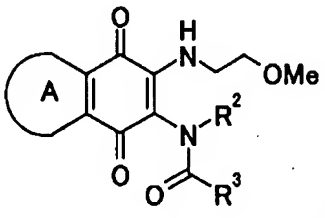
(IIe)

Ex	-R^1	-R^2	Sy	Dat
91	-$(CH_2)_3OMe$	-Me	2	N1: 1.7-2.0(5H,m), 2.92(3H,s), 3.25 (3H,s), 3.3-3.6(4H,m), 7.2-7.5(1H, m), 7.6-8.2(4H,m)
92	-$(CH_2)_3NMe_2$	-Me	2	F+: 330
93	-CH_2(Py2)	-Me	2	F+: 336 N1: 1.5-2.2(3H,m), 2.7-3.0(3H,m), 4.5-5.0(2H,m), 7.2-7.5(2H,m), 7.6-8.3(6H,m), 8.4-8.7(1H,m)
94	-CH_2(Py3)	-Me	2	F+: 336
95	-CH_2(Py4)	-Me	2	F+: 336
96	-CH_2CF_3	-Me	2	F+: 327
97	-CH_2Thf	-Me	2	F+: 329
98	- CH_2CONH_2	-Me	2	F+: 302
99	- CH_2CN	-Me	2	F+: 284
100		-Me	2	F+: 418
101		-Me	2	F': 399
102		-Me	2	F+: 357
103	-CH(Me)Ph	-$(CH_2)_2OMe$	2	F+: 375
104	-CH_2Pym	-$(CH_2)_2OMe$	2	F+: 381 N1: 1.61(3H,s), 3.08(3H,s), 3.2-3.9(4H,m), 4.6-5.0(2H,m), 7.4-7.6(1H, m), 7.7-8.1(5H,m), 8.75(1H,d), 9.12(1H,d)
105	-$(CH_2)_2OMe$	-CH_2Pyr	2	F+: 381 N1: 1.88(3H,s), 3.26(3H,s), 3.4-3.9(4H,m), 4.3-5.3(2H,m), 7.6-8.1(5H, m), 8.3-8.6(2H,m), 8.79(1H,d)
106	-CH_2(5-MePyr)	-$(CH_2)_2OMe$	2	F+: 395 N1: 1.61(3H,s), 2.47(3H,s), 3.07(3H,s), 3.2-3.8(4H,m), 4.6-5.0(2H,m), 7.7-8.1(5H,m), 8.4-8.6(2H,m)

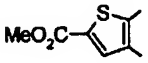
[0055]
[Table 12]

Ex	-R^1	-R^2	Sy	Dat
107	-CH_2Pyr	-CH_2Pyr	2	F+: 415 N1: 1.72(3H,s), 4.3-5.3(4H,m), 7.6-8.1(4H,m), 8.2-8.7(5H,m), 8.69(1H,s), 8.79(1H,s)
108	-CH_2(Py4)	-CH_2Pyr	2	F+: 414 N1: 1.58(3H,br), 4.2-5.1(4H,m), 7.29(2H,d), 7.6-8.1(4H,m), 8.28(1H,s), 8.3-8.7(4H,m), 8.78(1H,d)
109	-$(CH_2)_{17}$Me	-$(CH_2)_2$OMe	2	F+: 541
110	-CH_2Ad	-$(CH_2)_2$OMe	2	F: 437
111	-CH_2CHPh_2	-$(CH_2)_2$OMe	2	F: 469
112	-$(CH_2)_2O(CH_2)_2$OMe	-$(CH_2)_2$OMe	2	F: 391 N1: 1.84(3H,s), 3.0-3.9(18H,m), 6.9-7.2(1H,m), 7.7-7.9(2H,m), 7.9-8.1(2H,m)
113	-$(CH_2)_2O(CH_2)_2O(CH_2)_2$OMe	-$(CH_2)_2$OMe	2	F: 435
114	-$(CH_2)_2$O(4-BnO-Ph)	-$(CH_2)_2$OMe	2	F: 515

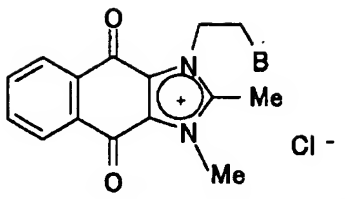
[0056]
[Table 13]



(IIg)

Ex	A	-R^2	-R^3	Sy	Dat
10		-Me	-CH_2NMe_2	-	F+: 346
11		-$(CH_2)_2$OMe	-Me	-	F+: 411
115		-Me	-CH_2Cl	2	F+: 337
116		-Me	-CH_2OMe	2	F+ 333
117		-$(CH_2)_4$-		2	F+: 329

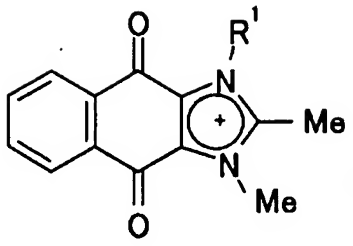
[0057]
[Table 14]



(Ia)

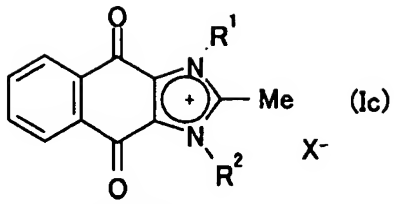
Ex	-B	Sal	Sy	Dat
6	-OH	-	-	F-: 270 N1: 2.90(3H,s), 3.8(2H,br), 4.17(3H,s), 4.74(2H,t), 7.9-8.2(4H,m)
118	-OMe	-	6	F: 285 N1: 2.89(3H,s), 3.25(3H,s), 3.77(2H,t), 4.20(3H,s), 4.8-5.0(2H,m), 7.9-8.3(4H,m)
119	-OPh	-	6	F-: 346 N1: 3.01(3H,s), 4.21(3H,s), 4.43(2H,t), 5.13(2H,t), 6.8-7.0(3H,m), 7.2-7.4(2H,m), 7.9-8.1(2H,m), 8.1-8.3(2H,m)
120	-OBn	-	6	F-: 360 N1: 2.89(3H,s), 3.90(2H,t), 4.19(3H,s), 4.45(2H,s), 4.89(2H,t), 7.1-7.5(5H,m), 7.9-8.1(2H,m), 8.1-8.3(2H,m)
121	-NMe_2	HCl	6	F: 298 N1: 2.8-3.0(6H,m), 3.02(3H,s), 3.5-3.8(2H,m), 4.16(3H,s), 5.0-5.2(2H,m), 7.9-8.1(2H,m), 8.1-8.3(2H,m), 11.2-11.5(1H,br)
122	-OEt	-	6	F: 299 N1: 1.06(3H,t), 2.89(3H,s), 3.44(2H,q), 3.80(2H,t), 4.20(3H,s), 4.86(2H,t), 7.9-8.1(2H,m), 8.1-8.3(2H,m)
123	-OPr	-	6	F: 313 N1: 0.80(3H,t), 1.3-1.6(2H,m), 2.90(3H,s), 3.35(2H,t), 3.80(2H,t), 4.20(3H,s), 4.87(2H,t), 7.9-8.1(2H,m), 8.1-8.3(2H,m)
124	-O(i-Pr)	-	6	F: 313 N1: 1.02(6H,d), 2.89(3H,s), 3.4-3.7(1H,m), 3.79(2H,t), 4.21(3H,s), 4.83(2H,t), 7.9-8.1(2H,m), 8.1-8.3(2H,m)
125	-$O(CH_2)_2NH_2$	HCl	6	F: 314
126	-OCH_2(Py3)	HCl	6	F: 362 N1: 2.90(3H,s), 3.98(2H,t), 4.21(3H,s), 4.68(2H,s), 4.95(2H,t), 7.8-8.1(3H,m), 8.1-8.4(3H,m), 8.6-8.9(2H,m)
127	-SMe	-	6	F: 301
128	-SO_2Me	-	6	F: 333
129	-NEt_2	HCl	6	E: 326
130	-$N(i\text{-}Pr)_2$	HCl	6	E: 354
131	-Pipe	HCl	6	E: 338
132	-Morp	HCl	6	E: 340

[0058]
[Table 15]



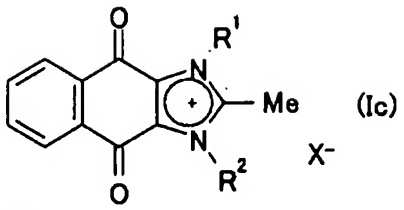
Ex	-R^1	Sal	Sy	Dat
133	-$(CH_2)_2NHAc$	-	6	F: 312 N1: 1.76(3H,s), 2.86(3H,s), 3.4-3.7(2H,m), 4.18(3H,s), 4.69(2H,t), 7.9-8.1(2H,m), 8.1-8.3(2H,m), 8.34(1H,t)
134	-$(CH_2)_2OCONHPh$	-	6	F: 390
135	-$(CH_2)_3OMe$	-	6	F: 299 N1: 2.0-2.2(2H,m), 2.88(3H,s), 3.24(3H,s), 3.42(2H,t), 4.18(3H,s), 4.69(2H,t), 7.9-8.1(2H,m), 8.1-8.3(2H,m)
136	-$(CH_2)_3NMe_2$	HCl	6	F: 312
137	-CH_2(Py2)	HCl	6	F: 318 N1: 2.96(3H,s), 4.25(3H,s), 6.14(2H,s), 7.3-7.6(1H,m), 7.72(1H,d), 7.8-8.3(5H,m), 8.53(1H,d)
138	-CH_2(Py3)	HCl	6	F: 318
139	-CH_2(Py4)	HCl	6	F: 318
140	-CH_2CF_3	-	6	F: 309
141	-$(CH_2)_2CONH_2$	-	6	F: 298
142	-$(CH_2)_2CN$	-	6	F: 280
143	-$(CH_2)_2O(CH_2)_2OMe$	-	6	F: 329
144	-CH_2Thf	-	6	F: 311
145	-CH_2CONH_2	-	6	F: 284
146	-CH_2CN	-	6	F: 266

[0059]
[Table 16]

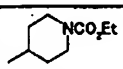


Ex	-R^1	-R^2	X	Sal	Sy	Dat
7	-Bn	-i-Pr	Br	-	-	F: 345 N1: 1.67(6H,d), 2.95(3H,s), 5.44(1H,br), 6.01(2H,s), 7.3-7.5(5H,m), 7.9-8.3(4H,m)
147	-Bn	-$(CH_2)_2$OH	Cl	-	6	F-: 346 N1: 2.88(3H,s), 3.86(2H,t), 4.75(2H,t), 6.02(2H,s), 7.3-7.5(5H,m), 7.9-8.3(4H,m)
148	-$(CH_2)_2$OMe	-$(CH_2)_2$OMe	Cl	-	6	F-: 328 N1: 2.89(3H,s), 3.24(6H,s), 3.78(4H,t), 4.87(4H,t), 7.9-8.1(2H,m), 8.1-8.3(2H,m)
149	-CH_2(Py4)	-Bn	Cl	HCl	6	F: 394
150	-CH_2(Py3)	-Bn	Cl	HCl	6	F: 394
151	-$(CH_2)_2$Ph	-$(CH_2)_2$OMe	Cl	-	6	F: 375
152	-CH_2Th	-$(CH_2)_2$OMe	Cl	-	6	F: 367
153	-CH_2Fu	-$(CH_2)_2$OMe	Cl	-	6	F: 351
154	-CH_2Pyr	-$(CH_2)_2$OMe	Cl	-	6	F: 363 N1: 2.8-3.2(6H,m), 3.84(2H,t), 4.92(2H,t), 6.19(2H,s), 7.8-8.0(2H,m), 8.0-8.2(2H,m), 8.52(1H,dd), 8.62(1H,d), 8.92(1H,d)
155	-CH_2Qu	-$(CH_2)_2$OMe	Cl	HCl	6	F: 412
156	-$(CH_2)_2$(Py2)	-$(CH_2)_2$OMe	Cl	HCl	6	F: 376
157	-$(CH_2)_2$(Py3)	-$(CH_2)_2$OMe	Cl	HCl	6	F: 376
158	-$(CH_2)_2$(Py4)	-$(CH_2)_2$OMe	Cl	HCl	6	F: 376
159	-$(CH_2)_2$In	-$(CH_2)_2$OMe	Cl	-	6	F: 414
160	-CH_2Dio	-$(CH_2)_2$OMe	Cl	-	6	F: 405
161	-$(CH_2)_3$Im	-$(CH_2)_2$OMe	Cl	HCl	6	F: 379 N1: 2.3-2.6(2H,m), 2.98(3H,s), 3.27(3H,s), 3.79(2H,t), 4.45(2H,t), 4.76(2H,t), 4.86(2H,t), 7.73(1H,d), 7.95(1H,d), 7.9-8.1(2H,m), 8.1-8.3(2H,m), 9.40(1H,s), 15.14(1H,br)
162	-$(CH_2)_2$Im	-$(CH_2)_2$OMe	Cl	HCl	6	F: 365 N1: 2.71(3H,s), 3.26(3H,s), 3.34(2H,t), 3.79(2H,t), 4.81(2H,t), 5.00(2H,t), 7.50(1H,s), 7.9-8.1(2H,m), 8.1-8.3(2H,m), 9.04(1H,s), 14.76(1H,br), 15.49(1H,br)
163	-CH_2Bim	-$(CH_2)_2$OMe	Cl	HCl	6	F: 401

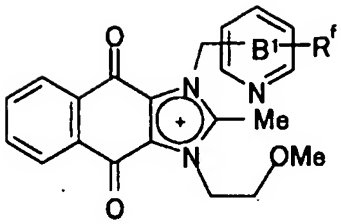
[0060]
[Table 17]



(Ic)

Ex	-R^1	-R^2	X	Sal	Sy	Dat
12	-$(CH_2)_2CO_2H$	-Me	Cl	-	-	F+: 299
164	-$(CH_2)_2O(CH_2)_2$-NH_2	-$(CH_2)_2$OMe	Cl	HCl	6	F: 358
165	-$(CH_2)_5NH_2$	-$(CH_2)_2$OMe	Cl	HCl	6	F: 356
166	-$(CH_2)_2O(CH_2)_2$-$O(CH_2)_2NH_2$	-$(CH_2)_2$OMe	Cl	HCl	6	F: 402
167	-CH(Me)Ph	-$(CH_2)_2$OMe	Cl	-	6	F: 375
168	-CH_2(5-MePyr)	-$(CH_2)_2$OMe	Cl	-	6	F: 377 N1: 2.99(3H,s), 3.27(3H,s), 3.82(2H,t), 4.92(2H,t), 6.13(2H,s), 7.9-8.1(2H,m), 8.1-8.3(2H,m), 8.4-8.5(1H,m), 8.7-8.9(1H,m)
169	-CH_2Pyr	-CH_2Pyr	Cl	-	6	F: 397 N1: 3.09(3H,br), 6.24(4H,br), 7.7-8.3(4H,m), 8.5-8.8(4H,m), 9.00(2H,d)
170	-CH_2(Py4)	-CH_2Pyr	Cl	-	6	F: 396 N1: 2.96(3H,s), 6.11(2H,s), 6.20(2H,s), 7.3-7.5(2H,m), 7.8-8.1(2H,m), 8.0-8.2(2H,m), 8.5-8.8(4H,m), 9.01(1H,d)
171		-Me	Cl	HCl	6	F: 400
172		-Me	Cl	-	6	F: 382
173		-Me	Cl	-	6	F: 339
174	-$(CH_2)_{17}$Me	-$(CH_2)_2$OMe	Cl	-	6	F: 523
175	-CH_2Ad	-$(CH_2)_2$OMe	Cl	-	6	F: 421
176	-CH_2CHPh_2	-$(CH_2)_2$OMe	Cl	-	6	F: 451
177	-$(CH_2)_2O(CH_2)_2$-OMe	-$(CH_2)_2$OMe	Cl	-	6	F: 373 N1: 2.91(3H,s), 3.15(3H,s), 3.24(3H,s), 3.3-3.4(2H,m), 3.4-3.6(2H,m), 3.79(2H,t), 3.87(2H,t), 4.7-5.0(4H,m), 7.9-8.1(2H,m), 8.1-8.3(2H,m)
178	-$(CH_2)_2O(CH_2)_2$-$O(CH_2)_2$OMe	-$(CH_2)_2$OMe	Cl	-	6	F: 417
179	-$(CH_2)_2$O(4-BnO-Ph)	-$(CH_2)_2$OMe	Cl	-	6	F: 497

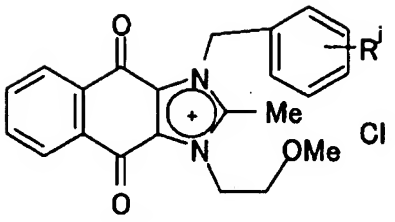
[0061]
[Table 18]



Cl - (Id)

Ex	B^1	$-R^f$	Sal	Sy	Dat
8	Py3	2-OH	-	-	F: 378
9	Py3	6-Cl	-	-	F: 396 N1: 2.91(3H,s), 3.25(3H,s), 3.79(2H,t), 4.86(2H,t), 6.05(2H,s), 7.59(1H,d), 7.87(1H,dd), 7.9-8.1(2H,m), 8.1-8.3(2H,m), 8.45(1H,d)
180	Py3	H	HCl	6	F: 362 N1: 2.93(3H,s), 3.26(3H,s), 3.80(2H,t), 4.88(2H,t), 6.16(2H,s), 7.8-8.3(6H,m), 8.7-8.9(2H,m)
181	Py2	H	HCl	6	F: 362 N1: 2.98(3H,s), 3.28(3H,s), 3.84(2H,t), 4.93(2H,t), 6.17(2H,s), 7.3-7.6(1H,m), 7.71(1H,d), 7.8-8.4(5H,m), 8.52(1H,d)
182	Py4	H	HCl	6	F: 362 N1: 2.92(3H,s), 3.28(3H,s), 3.83(2H,t), 4.92(2H,t), 6.35(2H,s), 7.9-8.3(6H,m), 8.98(2H,d)
183	Py3	1-oxide	HCl	6	F: 378
184	Py3	2-Cl	HCl	6	F: 396 N1: 2.92(3H,s), 3.28(3H,s), 3.84(2H,t), 4.93(2H,t), 6.03(2H,s), 7.3-7.6(2H,m), 7.9-8.0(2H,m), 8.0-8.3(2H,m), 8.42(1H,dd)
185	Py4	2-OH	-	8	F: 378 N1: 2.84(3H,s), 3.26(3H,s), 3.81(2H,t), 4.88(2H,t), 5.84(2H,s), 5.96(1H,s) ,6.22(1H,dd), 7.44(1H,d), 7.9-8.1(2H,m), 8.1-8.3(2H,m)
186	Py3	6-OMe	HCl	6	F: 392 N1: 2.92(3H,s), 3.24(3H,s), 3.7-4.0(5H,m), 4.6-5.5(2H,m), 5.97(2H,s), 6.87(1H,d), 7.75(1H,d), 7.9-8.1(2H,m), 8.1-8.4(3H,m)
187	Py3	2-NMe_2	HCl	6	F: 405
188	Py3	6-NMe_2	HCl	6	F: 405
189	Py3	5-Me	HCl	6	F: 376
190	Py3	6-Me	HCl	6	F: 376
191	Py3	6-CF_3	HCl	6	F: 430
192	Py4	2-Cl	HCl	6	F: 396 N1: 2.87(3H,s), 3.27(3H,s), 3.81(2H,t), 4.90(2H,t), 6.09(2H,s), 7.3-7.5(3H,m), 7.8-8.4(4H,m), 8.45(1H,d)
193	Py4	2-NMe_2	HCl	6	F: 405

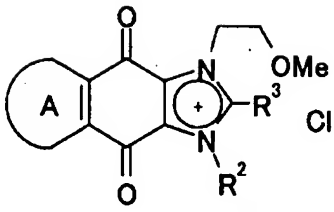
[0062]
[Table 19]

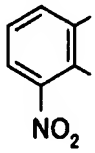
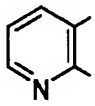
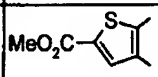


(Ie)

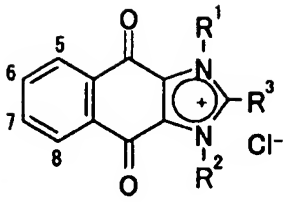
Ex	-R^j	Sal	Sy	Dat
194	H	-	6	F: 361 N1: 2.85(3H,s), 3.24(3H,s), 3.80(2H,t), 4.88(2H,t), 6.05(3H,s), 7.2-7.5(5H,m), 7.9-8.3(4H,m)
195	2-Cl	-	6	F: 395
196	3-Cl	-	6	F: 395
197	4-Cl	-	6	F: 395 N1: 2.85(3H,s), 3.24(3H,s), 3.79(2H,t), 4.86(2H,t), 6.02(2H,s), 7.34(2H,d), 7.48(2H,d), 7.9-8.1(2H,m), 8.1-8.3(2H,m)
198	3,4-Cl	-	6	F+: 431
199	2-OMe	-	6	F: 391
200	3-OMe	-	6	F: 391
201	4-OMe	-	6	F: 391
202	4-Ph	-	6	F: 437
203	3-CN	-	6	F: 386
204	4-CN	-	6	F: 386
205	4-SO_2NH_2	-	6	F: 440
206	4-CF_3	-	6	F: 429
207	4-F	-	6	F: 379 N1: 2.87(3H,s), 3.24(3H,s), 3.79(2H,t), 4.87(2H,t), 6.03(2H,s), 7.1-7.6(4H,m), 7.9-8.1(2H,m), 8.1-8.3(2H,m)
208	4-Br	-	6	F: 439, 441
209	3-CH_2NH_2	HCl	6	F: 390
210	4-CH_2NH_2	HCl	6	F: 390
211	3-NO_2	-	6	F: 406
212	4-NO_2	-	6	F: 406 N1: 2.87(3H,s), 3.26(3H,s), 3.81(2H,t), 4.89(2H,t), 6.18(2H,s), 7.61(2H,d), 7.9-8.4(6H,m)

[0063]
[Table 20]



Ex	A	-R^2	-R^3	Sal	Sy	Dat
213		-Me	$-CH_2OMe$	-	6	F: 315
214		-Me	$-CH_2NMe_2$	HCl	6	F: 328
215		$-(CH_2)_4-$		-	6	F: 311
216		$-(CH_2)_2OMe$	-Me	-	6	F: 374 N1: 2.90(3H,s), 3.72(2H,t), 3.77(2H,t), 4.81(2H,t), 4.87(2H,t), 8.1-8.5(3H,m)
217		$-(CH_2)_2OMe$	-Me	HCl	6	F: 330
218		$-(CH_2)_2OMe$	-Me	-	6	F: 393

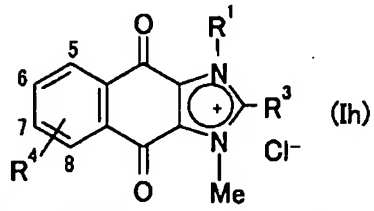
[0064]
[Table 21]



(Ig)

Co	R^1	R^2	R^3	Co	R^1	R^2	R^3
1	-CH_2CH=$CHCH_2OMe$	-$(CH_2)_2N(Bn)_2$	Me	18	-$(CH_2)_2OMe$	-$(CH_2)_2N(Me)COPh$	Me
2	-$(CH_2)_2OMe$	-$CH(Ph)CO_2Et$	Me	19	Me	-$(CH_2)_2NO_2$	Me
3	-$(CH_2)_2OMe$	-$(CH_2)_2SO_2NH_2$	Me	20	-$(CH_2)_2OMe$	-$(CH_2)_2CN$	Me
4	Me	-$(CH_2)_2SCH_2Ph$	Me	21	-$(CH_2)_2OMe$	-CH_2COPh	Me
5	-$(CH_2)_2OMe$	-$(CH_2)_2CO_2H$	Me	22	-$(CH_2)_2OMe$	-CH_2CONH_2	Me
6	-$(CH_2)_2OMe$	-$(CH_2)_2CO$(Pyr)	Me	23	-$(CH_2)_2OMe$	-$(CH_2)_2OAc$	Me
7	-$(CH_2)_2OMe$	-$(CH_2)_2CONH_2$	Me	24	Me	-$(CH_2)_2Ac$	Me
8	-$(CH_2)_2OMe$	-$(CH_2)_2N[(CH_2)_2NMe_2]_2$	Me	25	-$(CH_2)_2NH(CH_2)_2NH_2$	-$(CH_2)_2N(Me)Bn$	Me
9	-$(CH_2)_2OMe$	-$(CH_2)_2O(CH_2)_2NH(CH_2)_2NMe_2$	Me	26	-$(CH_2)_2OMe$	-$(CH_2)_2NHSO_2Me$	Me
10	-$(CH_2)_2OMe$	-$(CH_2)_2O$(Py4)	Me	27	-$(CH_2)_2OMe$	-$(CH_2)_2CONHOMe$	Me
11	-$CH_2C\equiv CCH_2OMe$	-$(CH_2)_2NHCONH_2$	Me	28	-$(CH_2)_2OMe$	-$(CH_2)_2OCOCH_2CO_2Et$	Me
12	-$(CH_2)_2OMe$	-$(CH_2)_2CO_2Me$	Me	29	Me	-$(CH_2)_2SOMe$	Me
13	-$(CH_2)_2OMe$	Me	CF_3	30	-$(CH_2)_2OMe$	Me	c-Pr
14	-CH_2(Pyr)	-$(CH_2)_2OMe$	H	31	Me	-$(CH_2)_2OMe$	-$(CH_2)_2OMe$
15	-$(CH_2)_2OMe$	-$(CH_2)_2O(CH_2)_2NMe_2$	Me	32	-$(CH_2)_2OMe$	-$(CH_2)_3O(CH_2)_2NMe_2$	Me
16	-$(CH_2)_2O$(c-Pr)	-$(CH_2)_2OMe$	Me	33	-$(CH_2)_2O$-$(CH_2)_2$(Morp)	-$(CH_2)_2OMe$	Me
17	-$(CH_2)_2OMe$	-$(CH_2)_2OCH_2$-		34	-$(CH_2)_2OMe$	-$(CH_2)_2N(Me)CH_2$-	

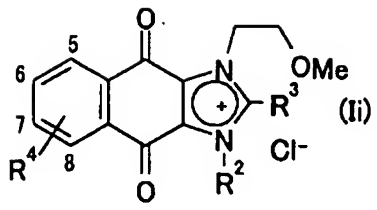
[0065]
[Table 22]



(Ih)

Co	R^1	R^3	R^4	Co	R^1	R^3	R^4
35	-CH_2(Py4)	Me	7-CF_3	37	-CH_2(Pyr)	H	6-NMe_2
36	-CH_2(Py3)	Me	5-CH_2NH_2	38	-$(CH_2)_2OMe$	Me	5-NO_2

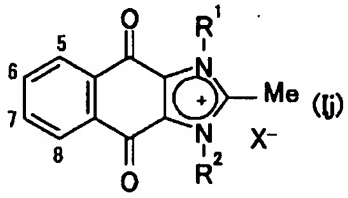
[0066]
[Table 23]



(Ii)

Co	R^2	R^3	R^4	Co	R^2	R^3	R^4
39	$-CH_2$(Pyr)	Me	5-F	57	$-CH_2$(Py4)	i-Pr	5-OMe
40	$-CH_2$(Py4)	Me	6-F	58	$-CH_2$(Py3)	Me	6-OMe
41	$-(CH_2)_2OMe$	Me	7-F	59	$-CH_2$(Pyr)	Me	7-OMe
42	$-CH_2$(Py3)	H	8-F	60	$-(CH_2)_2OMe$	Me	8-OMe
43	$-CH_2$(Pyr)	Me	8-CN	61	$-CH_2$(Py4)	Me	5-CN
44	$-CH_2$(Py3)	Me	5-CF_3	62	$-CH_2$(Py3)	Et	6-CN
45	$-(CH_2)_2OMe$	Et	6-CF_3	63	$-(CH_2)_2OMe$	Me	7-CN
46	$-(CH_2)_2OMe$	Me	5,8-OH	64	$-CH_2$(Pyr)	Me	8-CF_3
47	$-CH_2$(Py4)	Me	8-CH_2NH_2	65	$-(CH_2)_2OMe$	Me	5-CH_2N(Me)Bn
48	$-CH_2$(Py4)	Me	7-Me	66	$-(CH_2)_2OMe$	H	6-CH_2NH_2
49	$-CH_2$(Py3)	Me	8-Me	67	$-CH_2$(Pyr)	Me	7-CH_2NH_2
50	$-(CH_2)_2OMe$	Me	7-NMe_2	68	$-CH_2$(Py4)	Me	6-Me,7-F
51	$-CH_2$(Py4)	Me	8-NMe_2	69	$-CH_2$(Py3)	Me	5-NMe_2
52	$-CH_2$(Pyr)	Me	6,7-diMe	70	$-(CH_2)_2OMe$	Me	5,8-OMe
53	$-CH_2$(Py4)	H	6-NO_2	71	$-(CH_2)_2OMe$	Me	5-CH_2N(Me)COPh
54	$-(CH_2)_2OMe$	Me	5-Me	72	$-CH_2$(Py3)	Me	7-NO_2
55	$-CH_2$(Pyr)	i-Pr	6-Me	73	$-CH_2$(Pyr)	Me	8-NO_2
56	$-(CH_2)_2OMe$	Me	5-CH_2NMe_2	74	$-(CH_2)_2OMe$	Me	5-CH_2(Morp)

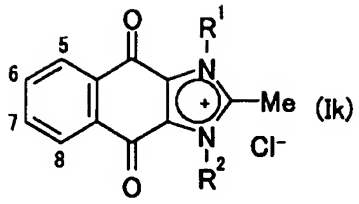
[0067]
[Table 24]

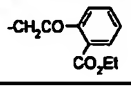
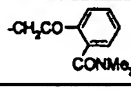
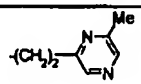
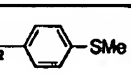
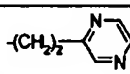
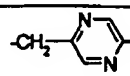
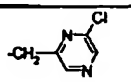
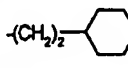
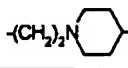
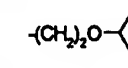
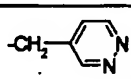
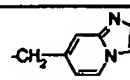
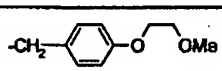
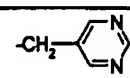
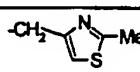
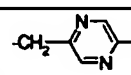
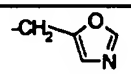
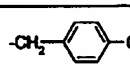
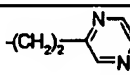
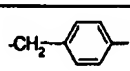
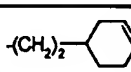
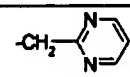
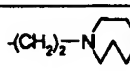
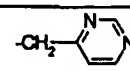
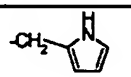
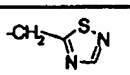
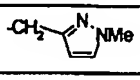
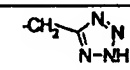
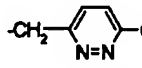
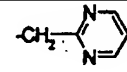
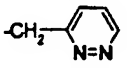
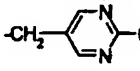
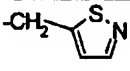
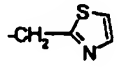


(Ij)

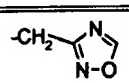
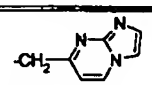
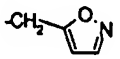
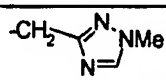
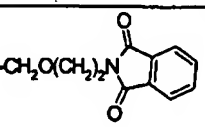
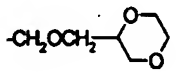
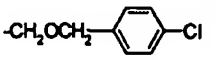
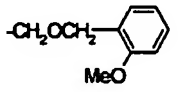
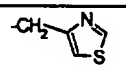
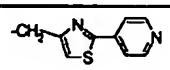
Co	R^1	R^2	X	Co	R^1	R^2	X
75	$-CH_2$(Pyr)	$-(CH_2)_2OMe$	Br	81	$-CH_2$(Pyr)	$-(CH_2)_2CO_2^-$	-
76	$-CH_2$(Py3)	$-(CH_2)_2OMe$	Br	82	$-CH_2$(Py4)	$-(CH_2)_2CO_2^-$	-
77	$-CH_2$(Py4)	$-(CH_2)_2OMe$	AcO	83	$-CH_2$(Py3)	$-CH_2CO_2^-$	-
78	$-CH_2$(Pyr)	$-(CH_2)_2OMe$	AcO	84	$-(CH_2)_2OMe$	$-CH_2CO_2^-$	-
79	$-CH_2$(Py3)	$-(CH_2)_2OMe$	$PhSO_3$	85	$-CH_2$(Py4)	$-(CH_2)_2OMe$	I
80	$-(CH_2)_2OMe$	$-(CH_2)_2OMe$	$PhSO_3$	86	$-(CH_2)_2OMe$	$-(CH_2)_2OMe$	I

[0068]
[Table 25]

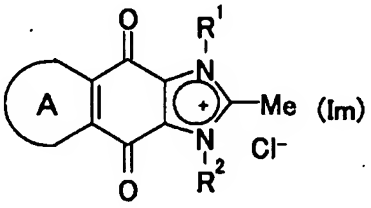


Co	R^1	R^2	Co	R^1	R^2
87	-$(CH_2)_2$OMe		104		-$(CH_2)_2$OMe
88		-$(CH_2)_2$OMe	105		-$(CH_2)_2$OMe
89	-$(CH_2)_2$OMe		106	-$(CH_2)_2$OMe	
90	-$(CH_2)_2$OMe		107	Me	
91	-$(CH_2)_2$OMe		108	-$(CH_2)_2$OMe	
92	-$(CH_2)_2$OMe		109	-$(CH_2)_2$OMe	
93	-$(CH_2)_2$OMe		110	-$(CH_2)_2$OMe	
94		-$(CH_2)_2$OMe	111		Me
95	-$(CH_2)_2$OMe		112	-$(CH_2)_2$OMe	
96	-$(CH_2)_2$OMe		113	-$(CH_2)_2$OMe	
97	-$(CH_2)_2$OMe		114	-$(CH_2)_2$OMe	
98	Me		115	-$(CH_2)_2$OMe	
99	-$(CH_2)_2$OMe		116		-$(CH_2)_2$OMe
100		-$(CH_2)_2$OMe	117	Me	
101	-$(CH_2)_2$OMe		118	-$(CH_2)_2$OMe	
102	-$(CH_2)_2$OMe		119		-$(CH_2)_2$OMe
103	Me		120		-$(CH_2)_2$OMe

[0069]
[Table 26]

Co	R^1	R^2	Co	R^1	R^2
121		$-(CH_2)_2OMe$	126	$-(CH_2)_2OMe$	
122	$-(CH_2)_2OMe$		127	$-(CH_2)_2OMe$	
123	$-(CH_2)_2OMe$		128	$-(CH_2)_2OMe$	
124	$-(CH_2)_2OMe$		129	$-(CH_2)_2OMe$	
125	$-(CH_2)_2OMe$		130		$-(CH_2)_2OMe$

[0070]
[Table 27]



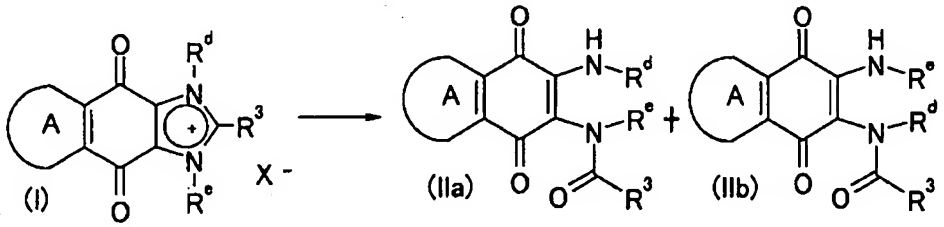
Co	R^1	R^2	A	Co	R^1	R^2	A
131	$-(CH_2)_2OMe$	$-(CH_2)_2OMe$		138	$-(CH_2)_2OMe$	$-(CH_2)_2OMe$	
132	$-(CH_2)_2OMe$	$-(CH_2)_2OMe$		139	$-(CH_2)_2OMe$	$-(CH_2)_2OMe$	
133	$-CH_2$(Py3)	$-(CH_2)_2OMe$		140	$-(CH_2)_2OMe$	$-CH_2$(Pyr)	
134	$-(CH_2)_2OMe$	$-(CH_2)_2OMe$		141	$-(CH_2)_2OMe$	$-(CH_2)_2OMe$	
135	$-CH_2$(Py3)	$-(CH_2)_2OMe$		142	$-CH_2$(Py4)	$-(CH_2)_2OMe$	
136	$-(CH_2)_2OMe$	$-(CH_2)_2OMe$		143	$-(CH_2)_2OMe$	$-(CH_2)_2OMe$	
137	$-(CH_2)_2OMe$	$-(CH_2)_2OMe$		144	$-(CH_2)_2OMe$	$-CH_2$(Py4)	

[Written Amendment]
[Filing Date] Heisei 14(2002) April 23 (2002. 4.23)
[Amendment 1]
[Document to be Amended] Description
[Item(s) to be Amended] 0015
[Method of Amendment] Change
[The contents of amendment]
[0015]
"OH formed into - prodrug" is the group in which the reversible prodrug inductor restored to a parent compound (hydroxy compound of a yuan) in the living body was formed -- for example, Prog. They are Med.5 and the group indicated to 2157-2161 (1985). the low-grade alkylene COOR (the following R

indicates H or low-grade alkyl to be -- the same) which may have a -OCO-substituent preferably - The low-grade alkenylene COOR which may have an OCO-substituent - The aryl, the -OCO low-grade alkylene O-low-grade alkylene COOR which may have an OCO-substituent - The low-grade alkylene COOR which may have the low-grade alkyl and -OSO2-substituent which may have OCO-CO-R and a -OCO-substituent, -O-lid RIJIRU, the 5-methyl 1, 3-dioxo ****- 2-****- 4-****- methyloxy, etc. are mentioned.

[Amendment 2]
[Document to be Amended] Description
[Item(s) to be Amended] 0025
[Method of Amendment] Change
[The contents of amendment]
[0025]
The 1st process
this invention compound (II) can be manufactured by making amines (V) react to a compound (IV) with a conventional method. Reactions are Chem.Pharm.Bull. and 44 (6), for example, 1181-1187 Tetrahedron.Lett., 39 (42), (1996) 7677-7678 (1998) Etc. -- [it Can Manufacture with the application of the Method of Description, and] the compound (IV) of the inside of suitable inert solvents (for example, benzene etc.), and a reaction equivalent amount, and (V) -- again -- yes -- using inorganic bases (potassium carbonate etc.) or organic bases suitable as an acid supplement agent (triethylamine etc.) if needed using an excessive quantity of gaps or one side -- ordinary temperature or warming -- it is advantageous to carry out in the bottom.
The 2nd process
With a conventional method, this invention compound (I) can manufacture this invention compound (II), cyclization and when the fourth class chlorinates. being able to perform a reaction with the application of the method of J.Org.Chem.USSR, 1, and given (1965) in 1479-85, for example, and using a reaction equivalent amount or an excessive quantity of acids among suitable inert solvents (for example, alcoholic solvent etc.) -- ordinary temperature or warming -- it is advantageous to carry out in the bottom.

[Amendment 3]
[Document to be Amended] Description
[Item(s) to be Amended] 0026
[Method of Amendment] Change
[The contents of amendment]
[0026]
The 3rd process
[Formula 10]



(Rd and Re show among a formula the arbitrary groups defined as R1 and R2.)
hydrolyzing this invention compound (I) with a conventional method -- two sorts of this invention compounds (IIa) -- and (IIb) it can obtain. The obtained compound can be further given to the modification reaction of a well-known group, and can also be made into the manufacture intermediate product of the desired this invention compound (I).
the hydrolysis reaction can apply the method of a description to J.Med.Chem., 7 (3), 362-364 (1964), etc., and a reaction equivalent amount or an excessive quantity of bases are used for it among water and a suitable inert solvent (for example, ethanol etc.), for example -- ordinary temperature or warming -- it is advantageous to carry out in the bottom. As a base, lithium hydroxide, sodium hydroxide, a potassium hydroxide, sodium carbonate, potassium carbonate, etc. are mentioned here.

[Amendment 4]
[Document to be Amended] Description
[Item(s) to be Amended] 0027
[Method of Amendment] Change
[The contents of amendment]
[0027]
The 4th process

this invention compound (III) can be manufactured in accordance with the method indicated to J.Med. Chem., 39 (7), 1447-1451 (1996), etc. from giving a compound (VI) to ring closure under existence of bases, such as sodium hydroxide.

The 5th process

this invention compound (I) can be manufactured by making a halide (VII) react to this invention compound (III), and considering it as the fourth class salt. a reaction can be performed with the application of the method of J.Med.Chem., 7 (3), and given (1964) in 362-364, for example -- desirable the compound (III) of the inside (for example, acetonitrile etc.) of a suitable inert solvent, and a reaction equivalent amount -- and (VII) -- again -- yes -- using an excessive quantity of gaps or one side -- ordinary temperature or warming -- the bottom can carry out under the flowing-back temperature of a solvent preferably.

Other manufacturing methods

this invention compound can also be manufactured by the modification reaction of the well-known substituent of versatility besides the above-mentioned process. For example, the compound which has the substituent including sulfonyl combination can be manufactured by oxidation reaction of a conventional method from the compound which has a sulfide bond or sulfinyl combination. Moreover, N-oxide inductor of the compound which has heteroaryl containing N atoms, such as a pyridyl machine, as a substituent can be manufactured by oxidation reaction of a conventional method. The compound which has the substituent containing carboxylic acid can be manufactured by the hydrolysis reaction of a conventional method from the compound which has ester or amide combination. The compound which has the substituent containing an amino alkyl group can be manufactured by the amination reaction of a conventional method from the compound which has a halogenation alkyl group. When it is this invention compound (II) and (III) educt, it can be considered as a salt by the salt formation reaction according to a conventional method by request.

[Amendment 5]

[Document to be Amended] Description

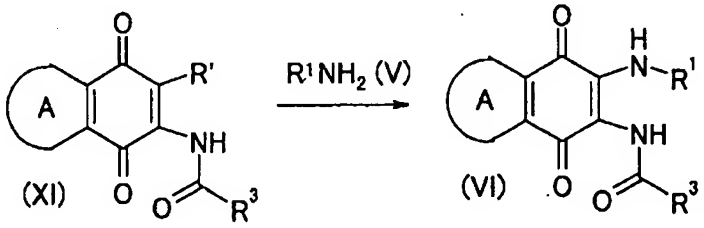
[Item(s) to be Amended] 0029

[Method of Amendment] Change

[The contents of amendment]

[0029]

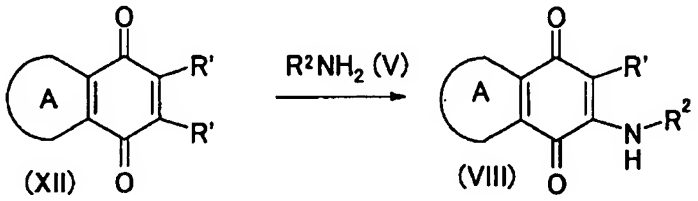
[Formula 13]



A compound (VI) can be manufactured according to amination of a compound (XI) in accordance with the method indicated to J.Med.Chem., 39 (7), 1447-1451 (1996), etc.

Synthetic process 4

[Formula 14]



Compounds (VIII) are J.Het.Chem., 33 (1), and 113-117 (1996), In accordance with the method indicated to Tetrahedron.Lett., 39 (42), 7677-7678 (1998), etc., it can manufacture according to amination of a compound (XII).

[Written Amendment]

[Filing Date] Heisei 14(2002) June 17 (2002. 6.17)

[Amendment 1]

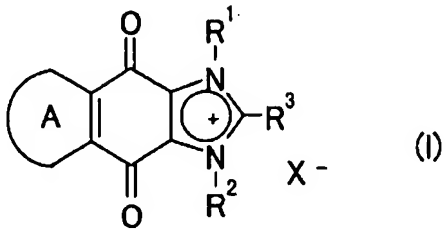
[Document to be Amended] Description

[Item(s) to be Amended] Claims

[Method of Amendment] Change

[The contents of amendment]

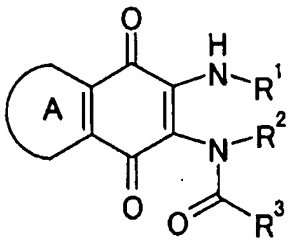
[Claim(s)]
[Claim 1] The condensation imidazolium inductor shown with a following general formula (I).
[Formula 1]



(I)

(The sign in a formula shows a following meaning.)
R1 and R2 : It is the same or different and - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (Low-grade alkynyl which has one or more substituents chosen from B group) - RinD, - low-grade alkyl, - low-grade ARUKENIRU, or - low-grade alkynyl, Either [at least] R1 or R2 However, - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (low-grade alkynyl which has one or more substituents chosen from B group), - (cycloalkyl which has one or more substituents), or - (5 which may have one or more substituents, or 7 member saturation heterocycle),
B group : -ORa, -SRa, OH formed into - prodrug, the -O-low-grade alkylene ORa, - The O-low-grade alkylene O-low-grade alkylene ORa, the -O-low-grade alkylene NRaRb, the -O-low-grade alkylene O-low-grade alkylene NRaRb, the -O-low-grade alkylene NRc-low-grade alkylene NRaRb, -OCO-NRaR b, -SORa, -SO2Ra, -SO2NRaRb, -NRa-SO2Rb, -NRaRb
The -NRc-low-grade alkylene NRaRb, -N(- low-grade alkylene NRaRb)2
-RinD, -NO2, -CN, - halogen, -CO2Ra, -COO-, -CONRaRb, -CONRa-O-Rb, -NRa-CORb, -NRa-CO-NRbR
c, -OCORa, and -CO-Ra,
Ra, Rb, and Rc: It is the same or different and they are -H, - low-grade alkyl, the - low-grade alkylene RinD, or -RinD,
RinD: - (5 which may have one or more substituents, or 7 member saturation heterocycle), - (Cycloalkyl which may have one or more substituents) - (cyclo ARUKENIRU which may have one or more substituents), - (aryl which may have one or more substituents), or - (heteroaryl which may have one or more substituents),
R3:-H -- or (low-grade alkyl which may have one or more substituents) -- or -- the low-grade alkylene of carbon numbers 2 to 5 which R2 and R3 are united and may be interrupted for O, S, or NR4 (R4:-H or - low-grade alkyl) may be formed
A ring: -- the heteroaryl ring which may have the aryl ring which may have one or more substituents, or one or more substituents -- and
X-: When counter anion, however substituent-COO- of B group and imidazolium ion form inner salt, X- does not exist.
However, R1 and R2 remove the compound which are the following combination.
(1) One side is - low-grade alkylene (aryl which may have one or more substituents), and another side is - CH3, -(CH2) 3CH3, or - phenyl,
(2) one side is - low-grade alkylene CO- (aryl which may have one or more substituents) -- another side - CH2CH(CH3)2 or -(CH2) 3CH3 -- or
(3) Both R1 and R2 are - benzyl and -(CH2) 2OC2H5 or -(CH2) 2.
O-COCH3.
[Claim 2] The 1-[(6-chloro 3-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
1, the 2-dimethyl 4, 9-dioxo 3-[(2-tetrahydrofuranyl) methyl]-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
1, the 3-bis(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 1-(2-pyrazinyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-[3-(1H-4-imidazolyl) propyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
3-(2-methoxy ethyl)-2-methyl 1-[(5-methyl 2-pyrazinyl) methyl]-4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 2-methyl 4, 9-dioxo 1, 3-bis(2-pyrazinyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-

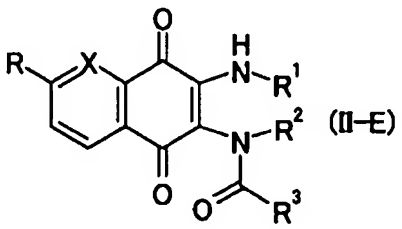
IUMU,
The 1-[2-(2-methoxyethoxy) ethyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-{2-[2-(2-methoxyethoxy) ethoxy] ethyl}-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 3-(3-pyridyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 1-(2-pyridyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 1-(4-pyridyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-[(2-chloro 3-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-[(2-hydroxy 4-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 3-(2-methoxy ethyl)-1-[(6-methoxy 3-pyridyl) methyl]-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-[(2-chloro 4-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-(4-chloro benzyl)-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-(4-fluoro benzyl)-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
1, 3-bis(2-methoxy ethyl)-2-methyl 5-nitroglycerine 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU
Or these tautomers and the condensation imidazolium inductor of the claim 1 description chosen from a salt with a halogen ion.
[Claim 3] The 2-acylamino 3-amino 1 and 4-quinone derivative which are shown with a following general formula (II), or its salt.
[Formula 2]

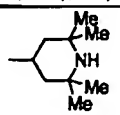


(II)

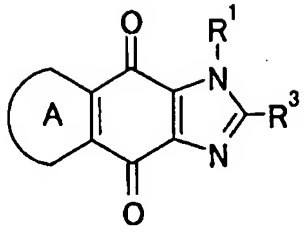
(The sign in a formula shows a following meaning.)
R1 and R2 : It is the same or different and - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (Low-grade alkynyl which has one or more substituents chosen from B group) - RinD, - low-grade alkyl, - low-grade ARUKENIRU, or - low-grade alkynyl, Either [at least] R1 or R2 However, - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (low-grade alkynyl which has one or more substituents chosen from B group), - (cycloalkyl which has one or more substituents), or - (5 which may have one or more substituents, or 7 member saturation heterocycle),
B group: -ORa, -SRa, OH formed into - prodrug, the -O-low-grade alkylene ORa, the -O-low-grade alkylene O-low-grade alkylene ORa, the -O-low-grade alkylene NRaRb, the -O-low-grade alkylene O-low-grade alkylene NRaRb
The -O-low-grade alkylene NRc-low-grade alkylene NRaRb, -OCO-NRa
The Rb, -SORa, -SO2Ra, -SO2NRaRb, -NRa-SO2Rb, -NRaRb, and -NRc-low-grade alkylene NRaRb, - N (- low-grade alkylene NRaRb)
2, -RinD, -NO2, -CN, - halogen, -CO2Ra, -CONRaRb
-CONRa-O-Rb, -NRa-CORb, -NRa-CO-NRbRc, -OCORa, and -CO-Ra,
Ra, Rb, and Rc: It is the same or different and they are -H, - low-grade alkyl, the - low-grade alkylene RinD, or -RinD,
RinD: - (5 which may have one or more substituents, or 7 member saturation heterocycle), - (Cycloalkyl which may have one or more substituents) - (cyclo ARUKENIRU which may have one or more substituents), - (aryl which may have one or more substituents), or - (heteroaryl which may have one or

more substituents),
R3:-H -- or (low-grade alkyl which may have one or more substituents) -- or -- the low-grade alkylene of carbon numbers 2 to 5 which R2 and R3 are united and may be interrupted for O, S, or NR4 (R4:-H or -low-grade alkyl) may be formed -- and
A ring: The heteroaryl ring which may have the aryl ring which may have one or more substituents, or one or more substituents.
However, the compound of the following table is removed.
[Table 1]



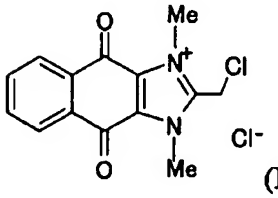
Comp	X	R	-R^1	-R^2	-R^3
E-1	CH	H	-Me	-CH_2-(3,4-Cl-Ph)	-Me
E-2	CH	H	-$CH(Me)_2$	-CH_2-(3,4-Cl-Ph)	-Me
E-3	CH	H	-CH_2-Ph	-(4-MeO-Ph)	-Me
E-4	CH	H	-CH_2-Ph	-(3-Br-Ph)	-Me
E-5	CH	H	-CH_2-Ph	-CH_2-(4-F-Ph)	-Me
E-6	CH	H	-$(CH_2)_2$-Ph	-CH_2-(4-F-Ph)	-Me
E-7	CH	H	-$(CH_2)_2$-OH	-Me	-Me
E-8	CH	H	-$(CH_2)_2$-OH	-CH_2-Ph	-Me
E-9	CH	H	-$(CH_2)_2$-OH	-(4-MeO-Ph)	-Me
E-10	CH	H	-$(CH_2)_2$-OH	-(4-MeCO-Ph)	-Me
E-11	CH	H	-$(CH_2)_2$-OH	-(3-Br-Ph)	-Me
E-12	CH	H	-$(CH_2)_2$-Cl	-CH_2CO_2Et	-Me
E-13	CH	H	-CH(Me)-CO_2H	-Me	-Me
E-14	CH	H	-CH(Me)-CONHMe	-Me	-Me
E-15	CH	H	-CH(Me)-CONHMe	-$CH(Me)_2$	-Me
E-16	CH	H	-CH(Me)-CONHMe		-Me
E-17	CH	H	-CH(Me)-CONHMe	-Me	-$(CH_2)_2$Me
E-18	CH	H	-CH(Me)-CONHMe	-Me	-$CH(Me)_2$
E-19	CH	H	-CH(Me)-CONHOMe	-Me	-Me
E-20	N	H	-CH(Me)-CONHMe	-Me	-Me
E-21	N	Me	-CH(Me)-CONHMe	-Me	-Me
E-22	CH	H		-Me	-Me

(-- the inside of front, and Comp -- a compound number -- Me -- a methyl group -- Et -- an ethyl group -- Ph -- a phenyl group -- moreover, in the case of a substitution phenyl group, a substituent is shown with a substitution position before Ph, for example, 3 and 4-Cl-Ph shows 3 and 4-dichlorophenyl.)
[Claim 4] The condensation imidazole derivative shown with a following general formula (III), or its salt.
[Formula 3]

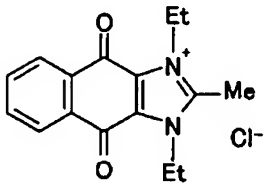


(III)

(The sign in a formula shows a following meaning.)
R1: - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - Or - (cycloalkyl which has one or more substituents), (Low-grade alkynyl which has one or more substituents chosen from B group) However, the low-grade alkyl group which has one or more substituents chosen from the group which consists of -NH2, -NMe2, -NEt2, -OH, - halogen, and - (phenyl which may be replaced by -Cl, -F, -Me, or -OMe) is excluded,
B group : -ORa, -SRa, OH formed into - prodrug, the -O-low-grade alkylene ORa, - The O-low-grade alkylene O-low-grade alkylene ORa, the -O-low-grade alkylene NRaRb, the -O-low-grade alkylene O-low-grade alkylene NRaRb, the -O-low-grade alkylene NRc-low-grade alkylene NRaRb, -OCO-NRaR b, -SORa, -SO2Ra, -SO2NRaRb, -NRa-SO2Rb, -NRaRb
The -NRc-low-grade alkylene NRaRb, -N(- low-grade alkylene NRaRb)2
-RinD, -NO2, -CN, - halogen, -CO2Ra, -CONRaRb, -CONRa-O-Rb, -NRa-CORb, -NRa-CO-NRbRc, -OCORa, and -CO-Ra,
Ra, Rb, and Rc: It is the same or different and they are -H, - low-grade alkyl, the - low-grade alkylene RinD, or -RinD,
RinD: - (5 which may have one or more substituents, or 7 member saturation heterocycle), - (Cycloalkyl which may have one or more substituents) - (cyclo ARUKENIRU which may have one or more substituents), - (aryl which may have one or more substituents), or - (heteroaryl which may have one or more substituents),
R3:-H -- or (low-grade alkyl which may have one or more substituents) -- and
A ring: Heteroaryl ring which may have the aryl ring which may have one or more substituents, or one or more substituents.
[Amendment 2]
[Document to be Amended] Description
[Item(s) to be Amended] 0002
[Method of Amendment] Change
[The contents of amendment]
[0002]
[Description of the Prior Art]
As the aryl ring or heteroaryl ring which has antitumor activity, and a condensed imidazolium inductor conventionally 4 of bottom type and 9-dioxo [2 and 3-naphth d] imidazolium compound (KP-1, KP-3 grade) is [only being indicated by Khim.Pharm.Zh., 32 (6), and 10-11 (1998) and].
[Formula 4]



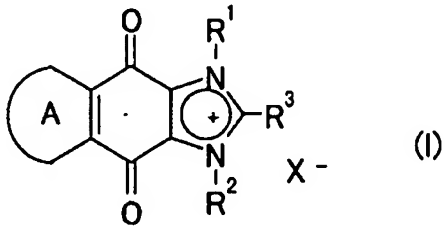
(KP-1)



(KP-3)

(Et shows ethyl among a formula and Me shows methyl, respectively.) the following -- the same .
J. [Med.Chem., 7 (3), and 362-364 (1964)] In the general formula (I) of after-mentioned this invention, both R1 and R2 are low-grade alkyl, or one side is - low-grade alkylene (aryl which may have one or more substituents), and another side is -CH3. - (CH2)
3CH3, the compound which is - phenyl group, or one side is - low-grade alkylene CO- (aryl which may have one or more substituents), and -CH2CH(CH3)2 or -(CH2) 3CH3, and the indication of a compound that comes out and has a certain antimicrobial action have another side. However, there is no indication about an anticancer operation.
[Amendment 3]
[Document to be Amended] Description
[Item(s) to be Amended] 0007

[Method of Amendment] Change
[The contents of amendment]
[0007]
That is, this invention relates to the condensation imidazolium inductor shown with a following general formula (I), and the condensation imidazolium inductor concerned.
[Formula 5]



(I)

(The sign in a formula shows a following meaning.)
R1 and R2 : It is the same or different and - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (Low-grade alkynyl which has one or more substituents chosen from B group) - RinD, - low-grade alkyl, - low-grade ARUKENIRU, or - low-grade alkynyl, Either [at least] R1 or R2 However, - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (low-grade alkynyl which has one or more substituents chosen from B group), - (cycloalkyl which has one or more substituents), or - (5 which may have one or more substituents, or 7 member saturation heterocycle),
B group : -ORa, -SRa, OH formed into - prodrug, the -O-low-grade alkylene ORa, - The O-low-grade alkylene O-low-grade alkylene ORa, the -O-low-grade alkylene NRaRb, the -O-low-grade alkylene O-low-grade alkylene NRaRb, the -O-low-grade alkylene NRc-low-grade alkylene NRaRb, -OCO-NRaR b, -SORa, -SO2Ra, -SO2NRaRb, -NRa-SO2Rb, -NRaRb
The -NRc-low-grade alkylene NRaRb, -N(- low-grade alkylene NRaRb)2
-RinD, -NO2, -CN, - halogen, -CO2Ra, -COO-, -CONRaRb, -CONRa-O-Rb, -NRa-CORb, -NRa-CO-NRbR
c, -OCORa, and -CO-Ra,
Ra, Rb, and Rc: It is the same or different and they are -H, - low-grade alkyl, the - low-grade alkylene RinD, or -RinD,
RinD: - (5 which may have one or more substituents, or 7 member saturation heterocycle), - (Cycloalkyl which may have one or more substituents) - (cyclo ARUKENIRU which may have one or more substituents), - (aryl which may have one or more substituents), or - (heteroaryl which may have one or more substituents),
R3: You may form the low-grade alkylene of carbon numbers 2 to 5 which -H, - (low-grade alkyl which may have one or more substituents), or R2 and R3 are united, and may be interrupted for O, S, or NR4 (R4:-H or - low-grade alkyl),
A ring: -- the heteroaryl ring which may have the aryl ring which may have one or more substituents, or one or more substituents -- and
X-: When counter anion, however substituent-COO- of B group and imidazolium ion form inner salt, X- does not exist.
However, R1 and R2 remove the compound which are the following combination.
(1) One side is - low-grade alkylene (aryl which may have one or more substituents), and another side is - CH3, -(CH2) 3CH3, or - phenyl,
(2) one side is - low-grade alkylene CO- (aryl which may have one or more substituents) -- another side - CH2CH(CH3)2 or -(CH2) 3CH3 -- or
(3) Both R1 and R2 are - benzyl and -(CH2) 2OC2H5 or -(CH2) 2 O-COCH3. the following -- the same .
[Amendment 4]
[Document to be Amended] Description
[Item(s) to be Amended] 0016
[Method of Amendment] Change
[The contents of amendment]
[0016]
- (5 which may have one or more substituents, or 7 member saturation heterocycle) - (cycloalkyl which may have one or more substituents), - (Si who has one or more substituents)
Clo alkyl, - (cyclo ARUKENIRU which may have one or more substituents), - (Aryl which may have

one or more substituents) Or although there is no restriction in particular as a substituent in - (heteroaryl which may have one or more substituents), they are 1-4 substituents preferably chosen from following C group.
C group: The - low-grade alkyl, - halogen, - halogeno low-grade alkyl, -ORa, and -O-low-grade alkylene ORa, -SRa, -NRaRb, -NO2, -CN, -CO2
The Ra, -CO-NRaRb, -CORa, -NRa-CORb, -SO2NRaRb, and - low-grade alkylene NRaRb, - aryl, - low-grade alkylene aryl, and -OCO-Ra (Ra and Rb show the same meaning as the above among a formula).
A still more desirable group among said C group - low-grade alkyl, - halogen, - halogeno low-grade alkyl, - OH, -O-low-grade alkyl, the -O-low-grade alkylene OH, -O-low-grade alkylene O-low-grade alkyl, - They are low-grade alkylene NH2, -NH2, -NH-low-grade alkyl, -N(low-grade alkyl)2, and - CO2H, -CO2-low-grade alkyl, -CO-NH2, -SO2-NH2, -NO2, and -CN. the following -- the same .
As a substituent in "the aryl ring which may have one or more substituents" in A ring, or "the heteroaryl ring which may have one or more substituents", preferably, the group of said C group is mentioned and a still more desirable group is the same as that of the above. It is -NO2 especially preferably.
[Amendment 5]
[Document to be Amended] Description
[Item(s) to be Amended] 0019
[Method of Amendment] Change
[The contents of amendment]

CONTINUE

For further translation, please click on the above button.
The current translation will be overwritten when you continue.

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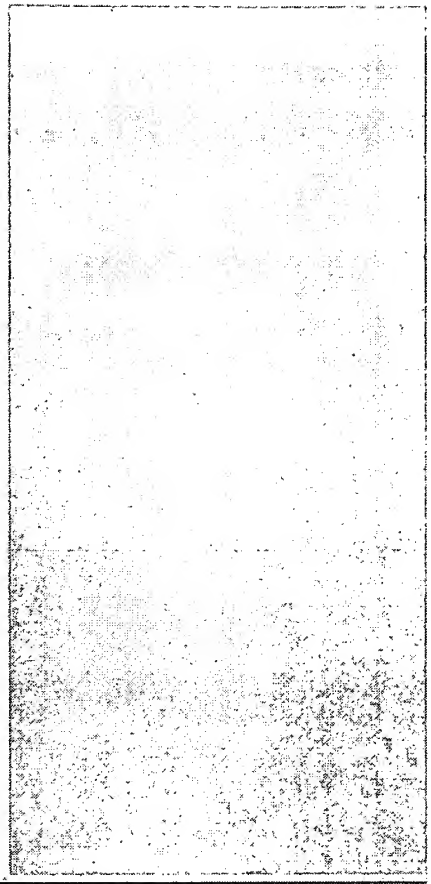


Report Mistranslation | Japanese (whole document in PDF)

[JP,01/060803,A1(2001)]

Japanese (PDF) | File Wrapper Information

FULL CONTENTS CLAIM + DETAILED DESCRIPTION WRITTEN AMENDMENT

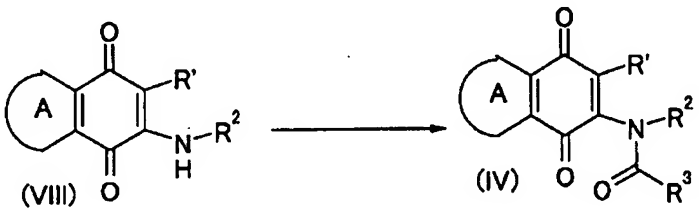
[Translation done.]

[Translation done.]

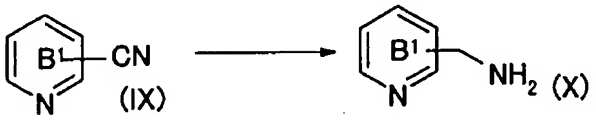
Continued translation.

[0019]
Moreover, desirable compound with the another this invention compound (I), R1 and R2 are the same or different, and - (low-grade alkyl which has one or more substituents chosen from B' group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B' group) - (Low-grade alkynyl which has one or more substituents chosen from B' group) - (Cycloalkyl which may have one or more substituents chosen from C' group) - (5 or 6 member monocycle heteroaryl which may have one or more substituents chosen from C' group) - (Aryl which may have one or more substituents chosen from C' group) - (5 or 7 member saturation heterocycle which may have one or more substituents chosen from C' group) - A low-grade alkylene (aryl which may have one or more substituents chosen from C' group), - low-grade alkylene CO- (aryl which may have one or more substituents chosen from C' group), and - either [low-grade alkyl and - low-grade ARUKENIRU or - low-grade alkynyl, however / at least] R1 or R2 - (low-grade alkyl which has one or more substituents chosen from B' group), - Or are - (low-grade alkynyl which has one or more substituents chosen from B' group), and (Low-grade ARUKENIRU which has one or more substituents chosen from B' group) [a;B' group] - ORa, -SRa, OH formed into - prodrug, the -O-low-grade alkylene RinD - SORa, -SO2Ra, -SO2NRaRb, NRa-SO2Rb, - The NRaRb and -NRc-low-grade alkylene RinD, -N(- low-grade alkylene RinD)2, and -NRc-low-grade alkylene NRaRb, -N(low-grade alkylene NRaRb)2 - (even if it has one or more substituents chosen from C' group) Good 5 or 7 member saturation heterocycle, - (5 which may have one or more substituents chosen from C' group, or 6 member monocycle heteroaryl), - Cycloalkyl, the -S-low-grade alkylene RinD, -NO2, -CN, - It is CO2Ra, -CONRaRb, -NRa-CORb, -OCORa, and -CO-low-grade alkyl and - CO- (5 which may have one or more substituents chosen from C' group, or 6 member monocycle heteroaryl),;Ra, and Rb and Rc are the same or different, and it is -H, - It is low-grade alkyl or -RinD, and;RinD - (5 which may have one or more substituents chosen from C' group, or 7 member saturation heterocycle) - Or are - (5 which may have one or more substituents chosen from C' group, or 6 member monocycle heteroaryl), and (Aryl which may have one or more substituents chosen from C' group) [a;C' group] - Low-grade alkyl and - halogen, -ORa, -SRa, -NRaRb, - NO2, -CN, -CO2Ra, -CO-NRaRb, - CORa, - Are NRa-CORb and -OCO-Ra, and;R3 are -H or - low-grade alkyl, and [;A ring] - It is the condensation imidazolium inductor; and whose X- it is benzene ring which may have the substituent chosen from the group which consists of low-grade alkyl and -ORa, -NRaRb, -CN, - halogen, and -NO2, and are counter anion.
[Amendment 6]
[Document to be Amended] Description
[Item(s) to be Amended] 0025
[Method of Amendment] Change
[The contents of amendment]
[0025]
The 1st process
this invention compound (II) can be manufactured by making amines (V) react to a compound (IV) with a conventional method. Reactions are Chem.Pharm.Bull. and 44 (6), for example, 1181-1187 Syn. Comm., 27 (12), (1996) 2143-2157 Tetrahedron.Lett., 39 (42), (1997) 7677-7678 (1998) Etc. -- [it Can Manufacture with the application of the Method of Description, and] the compound (IV) of the inside of suitable inert solvents (for example, benzene etc.), and a reaction equivalent amount, and (V) -- again -- yes -- using inorganic bases (potassium carbonate etc.) or organic bases suitable as an acid acceptor (triethylamine etc.) if needed using an excessive quantity of gaps or one side -- ordinary temperature or

warming -- it is advantageous to carry out in the bottom.
The 2nd process
With a conventional method, this invention compound (I) can manufacture this invention compound (II), cyclization and when the fourth class chlorinates. being able to perform a reaction with the application of the method of J.Org.Chem.USSR, 1, and given (1965) in 1479-85, for example, and using a reaction equivalent amount or an excessive quantity of acids among a suitable inert solvent (for example, alcoholic solvent) -- ordinary temperature or warming -- it is advantageous to carry out in the bottom.
[Amendment 7]
[Document to be Amended] Description
[Item(s) to be Amended] 0028
[Method of Amendment] Change
[The contents of amendment]
[0028]
Synthesis of a raw material compound
Some raw material compounds of this invention compound are new molecular entities, and these compounds can be easily compounded like a well-known raw material compound using a well-known method to a person skilled in the art. A typical synthetic process is shown below.
Synthetic process 1
[Formula 11]

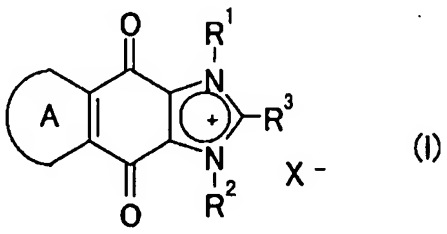


A compound (IV) is an acylation reaction of a conventional method to which a compound (VIII) is made to react with reactant carboxylic acid inductors, such as acid halide and an acid anhydride, for example in accordance with the method indicated to J.Org.Chem.USSR, 1, 1479-85 (1965), etc. It can manufacture. Synthetic process 2
[Formula 12]



(B1 shows among a formula the pyridine ring which may have a substituent.) the following -- the same . an aminomethyl pyridine inductor (X) -- the German patent No. 3726993 gazette (1989) etc. -- in accordance with the indicated method, it can manufacture by reduction of a compound (IX).
[Amendment 8]
[Document to be Amended] Description
[Item(s) to be Amended] 0039
[Method of Amendment] Change
[The contents of amendment]
[0039]
Example 5 of reference: Chlorination 2-chloro acetyl (3.3ml) was added to 1 of 2-chloro 1, 4-dihydro3-methylamino 1, and 4-dioxo naphthalene (2.2g), and 4-dioxane (30ml) solution, and it agitated under flowing back for 14 hours. The solvent was distilled off after cooling reaction mixture radiationally. The solid which added ethanol to the residue and deposited was ****(ed). The obtained solid was recrystallized from ethanol and 2-chloro N-(3-chloro 1, 4-dihydro1, 4-dioxo 2-naphtha RENIRU)-N-methyl acetamido (2.6g) of yellow powder was obtained.
Example 6 of reference: NaH (440mg) was added to the DMF (20ml) solution of the 2-oxo-piperidine (1.0g) 60%, and it agitated for 30 minutes at the room temperature. This solution was added to the DMF (150ml) solution of 2, 3-dichloro 1, 4-dihydro1, and 4-dioxo naphthalene (6.9g) at a stretch, and it agitated at the room temperature for 17 hours. Reaction mixture was opened in saturated ammonia water, the depositing solid was ****(ed), and ethyl acetate extracted filtrate. The organic layer was dried with anhydrous sodium sulfate after washing with water and saturation saline solution. Silica gel column chromatography (eluted with ethyl acetate hexane 1:10 solution) refined the residue after distilling off a solvent, and 2-chloro [of brown powder] 1, 4-dihydro1, and 4-dioxo 3-(2-oxo-piperidino) naphthalene (0.49g) was obtained.

[Amendment 9]
[Document to be Amended] Description
[Item(s) to be Amended] 0044
[Method of Amendment] Change
[The contents of amendment]
[0044]
Work example 9: They are 4M hydrogen chloride / ethyl acetate solution (10ml) to the ethanol (10ml) solution of N-{3-[(6-chloro 3-pyridyl) methyl] amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU}-N-(2-methoxy ethyl) acetamido (0.8g). In addition, it agitated for one day at the room temperature. Solvent **** and ethyl acetate wash a residue after distilling off. The chlorination 1-[(6-chloro 3-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4 of thin yellow powder, 9-dioxo 4, and 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU (0.82g) were obtained.
work example 10: They are 2M dimethyl amine / tetrahydrofuran solution (3.0ml) to the tetrahydrofuran (30ml) solution of 2-chloro N-[1, 4-dihydro3-(2-methoxy ethyl) amino 1, and 4-dioxo 2-naphtha RENIRU]-N-methyl acetamido (0.5g). In addition, it agitated at the room temperature for 18 hours. Water was added to reaction mixture and ethyl acetate extracted. The organic layer was dried with sulphuric anhydride magnesium after washing with water and saturation saline solution. The residue was crystallized from ethanol after distilling off a solvent, and N-[1, 4-dihydro3-(2-methoxy ethyl) amino 1, and 4-dioxo 2-naphtha RENIRU]-N-methyl 2-(dimethylamino) acetamido (0.19g) of brown powder was obtained.
Work example 11: It is 2-methoxy ethylamine (0.15ml) to the tetrahydrofuran (30ml) solution of 5-[N-acetyl N-(2-methoxy ethyl) amino]-4, 7-dihydro4, and 7-dioxo [benzob] thiophene 2-carboxylic acid methyl (0.39g). In addition, it agitated at the room temperature for 6.5 hours. Solvent Silica gel column chromatography (eluted with hexane ethyl acetate 50:1 solution) refines a residue after distilling off. Purplish red color oil-like 4 [5-[N-acetyl N-(2-methoxy ethyl) amino]-], the 7-dihydro6-(2-methoxy ethyl) amino 4, and 7-dioxo [benzob] thiophene 2-carboxylic acid methyl (0.39g) were obtained.
Work example 12: They are 4M hydrogen chloride / ethyl acetate solution (2.5ml) to the methanol (30ml) suspension of 3-{[4[the 3-(N-acetyl N-methyl) amino 1, 4-dihydro1, and]-dioxo 2-naphtha RENIRU] Amino} pro PIONAMIDO (0.32g). In addition, it agitated at the room temperature for 16 hours. The solvent was distilled off and heating churning of the residue was carried out in ethanol. The produced precipitation was washed by **** and ethanol after radiationnal cooling, and chlorination 1-(2-carboxyethyl)-4 in end of non-color powder, 9-dihydro2, 3-dimethyl 4, and 9-dioxo 1H-[2 and 3-naphth d] imidazole 3-IUMU (0.15g) was obtained.
The work-example compound of the description was obtained to the after-mentioned tables 6-20 like the above-mentioned work examples 1-9.
The constitutional formula and physicochemical character of a work-example compound are shown in the after-mentioned tables 3-5 in Tables 6-20 at the row of the example compound of reference, respectively. Moreover, almost like a method given in said work example or a manufacturing method, the compound [thing mentioned above / Tables 21-27 / a compound / a chemical structure type] applies some obvious strange method to a person skilled in the art at them, or is manufactured easily.
[Written Amendment]
[Filing Date] Heisei 14(2002) July 30 (2002. 7.30)
[Amendment 1]
[Document to be Amended] Description
[Item(s) to be Amended] Claims
[Method of Amendment] Change
[The contents of amendment]
[Claim(s)]
[Claim 1] The condensation imidazolium inductor shown with a following general formula (I).
[Formula 1]

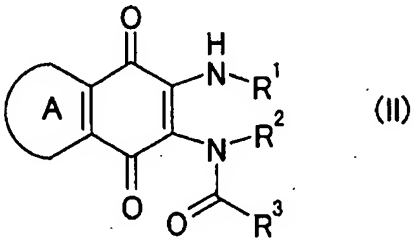


(I)

(The sign in a formula shows a following meaning.)
R1 and R2 : It is the same or different and - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) -

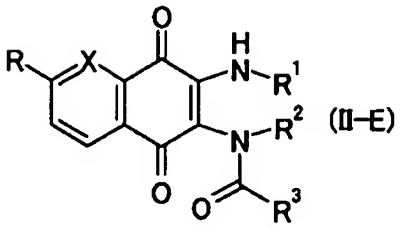
(Low-grade alkynyl which has one or more substituents chosen from B group) - RinD, - low-grade alkyl, - low-grade ARUKENIRU, or - low-grade alkynyl, Either [at least] R1 or R2 However, - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (low-grade alkynyl which has one or more substituents chosen from B group), - (cycloalkyl which has one or more substituents), or - (5 which may have one or more substituents, or 7 member saturation heterocycle),
B group : -ORa, -SRa, OH formed into - prodrug, the -O-low-grade alkylene ORa, - The O-low-grade alkylene O-low-grade alkylene ORa, the -O-low-grade alkylene NRaRb, the -O-low-grade alkylene O-low-grade alkylene NRaRb, the -O-low-grade alkylene NRc-low-grade alkylene NRaRb, -OCO-NRaR b, -SORa, -SO2Ra, -SO2NRaRb, -NRa-SO2Rb, -NRaRb
The -NRc-low-grade alkylene NRaRb, -N(- low-grade alkylene NRaRb)2
-RinD, -NO2, -CN, - halogen, -CO2Ra, -COO-, -CONRaRb, -CONRa-O-Rb, -NRa-CORb, -NRa-CO-NRbR
c, -OCORa, and -CO-Ra,
Ra, Rb, and Rc: It is the same or different and they are -H, - low-grade alkyl, the - low-grade alkylene RinD, or -RinD,
RinD: - (5 which may have one or more substituents, or 7 member saturation heterocycle), - (Cycloalkyl which may have one or more substituents) - (cyclo ARUKENIRU which may have one or more substituents), - (aryl which may have one or more substituents), or - (heteroaryl which may have one or more substituents),
R3:-H -- or (low-grade alkyl which may have one or more substituents) -- or -- the low-grade alkylene of carbon numbers 2 to 5 which R2 and R3 are united and may be interrupted for O, S, or NR4 (R4:-H or - low-grade alkyl) may be formed
A ring: -- the heteroaryl ring which may have the aryl ring which may have one or more substituents, or one or more substituents -- and
X-: When counter anion, however substituent-COO- of B group and imidazolium ion form inner salt, X- does not exist.
However, R1 and R2 remove the compound which are the following combination.
(1) One side is - low-grade alkylene (aryl which may have one or more substituents), and another side is - CH3, -(CH2) 3CH3, or - phenyl,
(2) one side is - low-grade alkylene CO- (aryl which may have one or more substituents) -- another side - CH2CH(CH3)2 or -(CH2) 3CH3 -- or
(3) Both R1 and R2 are - benzyl and -(CH2) 2OC2H5 or -(CH2) 2.
O-COCH3.
[Claim 2] The 1-[(6-chloro 3-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
1, the 2-dimethyl 4, 9-dioxo 3-[(2-tetrahydrofuranyl) methyl]-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
1, the 3-bis(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 1-(2-pyrazinyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-[3-(1H-4-imidazolyl) propyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
3-(2-methoxy ethyl)-2-methyl 1-[(5-methyl 2-pyrazinyl) methyl]-4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 2-methyl 4, 9-dioxo 1, 3-bis(2-pyrazinyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-[2-(2-methoxyethoxy) ethyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-{2-[2-(2-methoxyethoxy) ethoxy] ethyl}-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 3-(3-pyridyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 1-(2-pyridyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 1-(4-pyridyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-[(2-chloro 3-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-[(2-hydroxy 4-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,

The 3-(2-methoxy ethyl)-1-[(6-methoxy 3-pyridyl) methyl]-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-[(2-chloro 4-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-(4-chloro benzyl)-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-(4-fluoro benzyl)-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
1, 3-bis(2-methoxy ethyl)-2-methyl 5-nitroglycerine 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU
Or these tautomers and the condensation imidazolium inductor according to claim 1 chosen from a salt with a halogen ion.
[Claim 3] The 2-acylamino 3-amino 1 and 4-quinone derivative which are shown with a following general formula (II), or its salt.
[Formula 2]

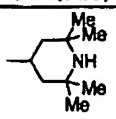


(II)

(The sign in a formula shows a following meaning.)
R1 and R2 : It is the same or different and - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (Low-grade alkynyl which has one or more substituents chosen from B group) - RinD, - low-grade alkyl, - low-grade ARUKENIRU, or - low-grade alkynyl, Either [at least] R1 or R2 However, - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - (low-grade alkynyl which has one or more substituents chosen from B group), - (cycloalkyl which has one or more substituents), or - (5 which may have one or more substituents, or 7 member saturation heterocycle),
B group: -ORa, -SRa, OH formed into - prodrug, the -O-low-grade alkylene ORa, the -O-low-grade alkylene O-low-grade alkylene ORa, the -O-low-grade alkylene NRaRb, the -O-low-grade alkylene O-low-grade alkylene NRaRb
The -O-low-grade alkylene NRc-low-grade alkylene NRaRb, -OCO-NRa
The Rb, -SORa, -SO2Ra, -SO2NRaRb, -NRa-SO2Rb, -NRaRb, and -NRc-low-grade alkylene NRaRb, - N (- low-grade alkylene NRaRb)
2, -RinD, -NO2, -CN, - halogen, -CO2Ra, -CONRaRb
-CONRa-O-Rb, -NRa-CORb, -NRa-CO-NRbRc, -OCORa, and -CO-Ra,
Ra, Rb, and Rc: It is the same or different and they are -H, - low-grade alkyl, the - low-grade alkylene RinD, or -RinD,
RinD: - (5 which may have one or more substituents, or 7 member saturation heterocycle), - (Cycloalkyl which may have one or more substituents) - (cyclo ARUKENIRU which may have one or more substituents), - (aryl which may have one or more substituents), or - (heteroaryl which may have one or more substituents),
R3:-H -- or (low-grade alkyl which may have one or more substituents) -- or -- the low-grade alkylene of carbon numbers 2 to 5 which R2 and R3 are united and may be interrupted for O, S, or NR4 (R4:-H or - low-grade alkyl) may be formed -- and
A ring: The heteroaryl ring which may have the aryl ring which may have one or more substituents, or one or more substituents.
However, the compound of the following table is removed.
[Table 1]



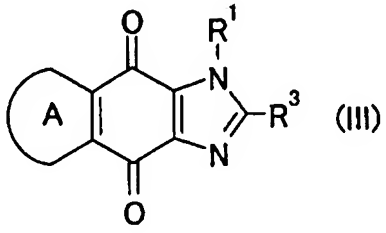
(II-E)

Comp	X	R	-R1	-R2	-R3
E-1	CH	H	-Me	-CH_2-(3,4-Cl-Ph)	-Me
E-2	CH	H	-$CH(Me)_2$	-CH_2-(3,4-Cl-Ph)	-Me
E-3	CH	H	-CH_2-Ph	-(4-MeO-Ph)	-Me
E-4	CH	H	-CH_2-Ph	-(3-Br-Ph)	-Me
E-5	CH	H	-CH_2-Ph	-CH_2-(4-F-Ph)	-Me
E-6	CH	H	-$(CH_2)_2$-Ph	-CH_2-(4-F-Ph)	-Me
E-7	CH	H	-$(CH_2)_2$-OH	-Me	-Me
E-8	CH	H	-$(CH_2)_2$-OH	-CH_2-Ph	-Me
E-9	CH	H	-$(CH_2)_2$-OH	-(4-MeO-Ph)	-Me
E-10	CH	H	-$(CH_2)_2$-OH	-(4-MeCO-Ph)	-Me
E-11	CH	H	-$(CH_2)_2$-OH	-(3-Br-Ph)	-Me
E-12	CH	H	-$(CH_2)_2$-Cl	-CH_2CO_2Et	-Me
E-13	CH	H	-CH(Me)-CO_2H	-Me	-Me
E-14	CH	H	-CH(Me)-CONHMe	-Me	-Me
E-15	CH	H	-CH(Me)-CONHMe	-$CH(Me)_2$	-Me
E-16	CH	H	-CH(Me)-CONHMe		-Me
E-17	CH	H	-CH(Me)-CONHMe	-Me	-$(CH_2)_2Me$
E-18	CH	H	-CH(Me)-CONHMe	-Me	-$CH(Me)_2$
E-19	CH	H	-CH(Me)-CONHOMe	-Me	-Me
E-20	N	H	-CH(Me)-CONHMe	-Me	-Me
E-21	N	Me	-CH(Me)-CONHMe	-Me	-Me
E-22	CH	H		-Me	-Me

(-- the inside of front, and Comp -- a compound number -- Me -- a methyl group -- Et -- an ethyl group -- Ph -- a phenyl group -- moreover, in the case of a substitution phenyl group, a substituent is shown with a substitution position before Ph, for example, 3 and 4-Cl-Ph shows 3 and 4-dichlorophenyl.)

[Claim 4] The condensation imidazole derivative shown with a following general formula (III), or its salt.

[Formula 3]

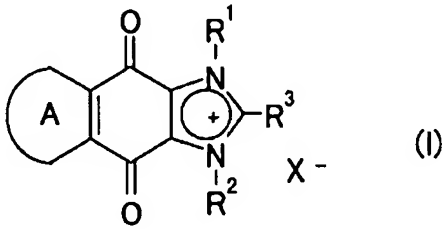


(III)

(The sign in a formula shows a following meaning.)

R1: - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) - Or - (cycloalkyl which has one or more substituents), (Low-grade alkynyl which has one or more substituents chosen from B group)

However, the low-grade alkyl group which has one or more substituents chosen from the group which consists of -NH2, -NMe2, -NEt2, -OH, - halogen, and - (phenyl which may be replaced by -Cl, -F, -Me, or -OMe) is excluded,
B group : -ORa, -SRa, OH formed into - prodrug, the -O-low-grade alkylene ORa, - The O-low-grade alkylene O-low-grade alkylene ORa, the -O-low-grade alkylene NRaRb, the -O-low-grade alkylene O-low-grade alkylene NRaRb, the -O-low-grade alkylene NRc-low-grade alkylene NRaRb, -OCO-NRaR b, -SORa, -SO2Ra, -SO2NRaRb, -NRa-SO2Rb, -NRaRb
The -NRc-low-grade alkylene NRaRb, -N(- low-grade alkylene NRaRb)2
-RinD, -NO2, -CN, - halogen, -CO2Ra, -CONRaRb, -CONRa-O-Rb, -NRa-CORb, -NRa-CO-NRbRc, -OCORa, and -CO-Ra,
Ra, Rb, and Rc: It is the same or different and they are -H, - low-grade alkyl, the - low-grade alkylene RinD, or -RinD,
RinD: - (5 which may have one or more substituents, or 7 member saturation heterocycle), - (Cycloalkyl which may have one or more substituents) - (cyclo ARUKENIRU which may have one or more substituents), - (aryl which may have one or more substituents), or - (heteroaryl which may have one or more substituents),
R3:-H -- or (low-grade alkyl which may have one or more substituents) -- and
A ring: Heteroaryl ring which may have the aryl ring which may have one or more substituents, or one or more substituents.
[Written Amendment]
[Filing Date] Heisei 14(2002) November 8 (2002. 11.8)
[Amendment 1]
[Document to be Amended] Description
[Item(s) to be Amended] Whole sentence
[Method of Amendment] Change
[The contents of amendment]
[Title of the Invention] Condensation imidazolium inductor
[Claim(s)]
[Claim 1] The condensation imidazolium inductor shown with a following general formula (I).
[Formula 1]

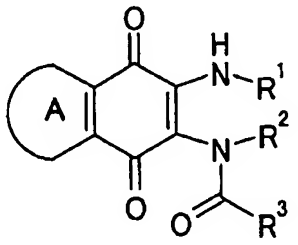


(I)

(The sign in a formula shows a following meaning.)
R1 and R2: Either is -O-low-grade alkyl and a -O-low-grade alkylene.
RinD, -O-RinD, -S-low-grade alkyl, the -S-low-grade alkylene Ri
The nD, -S-RinD, and -O-low-grade alkylene ORa, the -O-low-grade alkylene O-low-grade alkylene ORa, - NRa-low-grade alkyl, the -NRa-low-grade alkylene RinD, -NRa-RinD, - NRa-CO-low-grade alkyl, the -NRa-CO-low-grade alkylene RinD, -NRa-CO-RinD, -(5 which may have one or more substituents chosen from C group, or 7 member saturation heterocycle)- (C)
Cycloalkyl and - which may have one or more substituents chosen from a group
the heteroaryl which may have one or more substituents chosen from C group -- from
It is low-grade alkyl which has one or more substituents chosen from ****.;
Another side - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) They are - (low-grade alkynyl which has one or more substituents chosen from B group), -RinD, - low-grade alkyl, - low-grade ARUKENIRU, or - low-grade alkynyl,
B group : -ORa, -SRa, OH formed into - prodrug, the -O-low-grade alkylene ORa, - The O-low-grade alkylene O-low-grade alkylene ORa, the -O-low-grade alkylene NRaRb, the -O-low-grade alkylene O-low-grade alkylene NRaRb, the -O-low-grade alkylene NRc-low-grade alkylene NRaRb, -OCO-NRaR b, -SORa, -SO2Ra, -SO2NRaRb, -NRa-SO2Rb, -NRaRb
The -NRc-low-grade alkylene NRaRb, -N(- low-grade alkylene NRaRb)2
-RinD, -NO2, -CN, - halogen, -CO2Ra, -COO-, -CONRaRb, -CONRa-O-Rb, -NRa-CORb, -NRa-CO-NRbR
c, -OCORa, and -CO-Ra,
- Low-grade Al who may have the prodrug-ized OH:-OCO-substituent

Low-grade alkenylene C which may have Killen COOR and a -OCO-substituent
Aryl, -OCO low-grade ARUKIRE which may have OOR and a -OCO-substituent
The **- O-low-grade alkylene COOR, -OCO-CO-R, and a -OCO-substituent
The low-grade alkylene COOR which may have the low-grade alkyl and -OSO2-substituent which you may have, -O-lid RIJIRU, the 5-methyl 1, 3-dioxo ****-
2-****- 4-****- methyloxy,
R: H or low-grade alkyl,
Ra, Rb, and Rc: It is the same or different and they are -H, - low-grade alkyl, the - low-grade alkylene RinD, or -RinD,
RinD: - (5 which may have one or more substituents chosen from C group, or 7 member saturation heterocycle), - (Cycloalkyl which may have one or more substituents chosen from C group) - (Cyclo ARUKENIRU which may have one or more substituents chosen from C group) - (aryl which may have one or more substituents chosen from C group), or - (heteroaryl which may have one or more substituents chosen from C group),
C group: - low-grade alkyl, - halogen, - halogeno low-grade alkyl, -ORa1 -
O-low-grade alkylene ORa1, -SRa1, -NRa1Rb1, -NO2, -CN, -CO2Ra1, -CO-NRa1Rb1, -CORa1, -NRa1-CORb1, -SO2N
Ra1Rb1, - low-grade alkylene NRa1Rb1, - aryl, - low-grade Al ******-**
A reel and -OCO-Ra1,
Ra1 and Rb1: It is the same or different and they are -H or - low-grade alkyl,
R3:-H -- or (- halogen, -ORa1, -SRa1, -NRa1Rb1, -NO2 **)
You may form the low-grade alkylene of carbon numbers 2 to 5 which the low-grade alkyl which may have one or more substituents chosen from **-CN, or R2 and R3 are united, and may be interrupted for O, S, or NR4 (R4:-H or - low-grade alkyl),
A ring: -- benzene ring which may have one or more substituents chosen from C group -- and
X-: When counter anion, however substituent-COO- of B group and imidazolium ion form inner salt, X- does not exist.
However, both R1 and R2 remove the compound which is an ethoxyethyl machine.
[Claim 2] The 1-[(6-chloro 3-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
1, the 2-dimethyl 4, 9-dioxo 3-[(2-tetrahydrofuranyl) methyl]-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
1, the 3-bis(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 1-(2-pyrazinyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-[3-(1H-4-imidazolyl) propyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
3-(2-methoxy ethyl)-2-methyl 1-[(5-methyl 2-pyrazinyl) methyl]-4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 2-methyl 4, 9-dioxo 1, 3-bis(2-pyrazinyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-[2-(2-methoxyethoxy) ethyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-{2-[2-(2-methoxyethoxy) ethoxy] ethyl}-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 3-(3-pyridyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 1-(2-pyridyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 1-(4-pyridyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-[(2-chloro 3-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-[(2-hydroxy 4-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 3-(2-methoxy ethyl)-1-[(6-methoxy 3-pyridyl) methyl]-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-[(2-chloro 4-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
The 1-(4-chloro benzyl)-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,

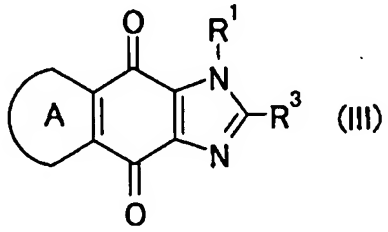
The 1-(4-fluoro benzyl)-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU,
1, 3-bis(2-methoxy ethyl)-2-methyl 5-nitroglycerine 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU
Or these tautomers and the condensation imidazolium inductor according to claim 1 chosen from a salt with a halogen ion.
[Claim 3] The 2-acylamino 3-amino 1 and 4-quinone derivative which are shown with a following general formula (II), or its salt.
[Formula 2]



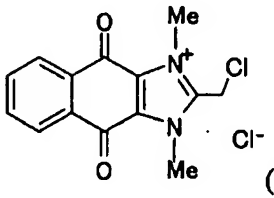
(II)

(The sign in a formula shows a following meaning.)
R1 and R2: Either is -O-low-grade alkyl and a -O-low-grade alkylene.
RinD, -O-RinD, -S-low-grade alkyl, the -S-low-grade alkylene Ri
The nD, -S-RinD, and -O-low-grade alkylene ORa, the -O-low-grade alkylene O-low-grade alkylene ORa, - NRa-low-grade alkyl, the -NRa-low-grade alkylene RinD, -NRa-RinD, - NRa-CO-low-grade alkyl, the -NRa-CO-low-grade alkylene RinD, -NRa-CO-RinD, -(5 which may have one or more substituents chosen from C group, or 7 member saturation heterocycle)- (C)
Cycloalkyl and - which may have one or more substituents chosen from a group
From heteroaryl to ** which may have one or more substituents chosen from C group
It is low-grade alkyl which has one or more substituents **(ed).;
Another side - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) They are - (low-grade alkynyl which has one or more substituents chosen from B group), -RinD, - low-grade alkyl, - low-grade ARUKENIRU, or - low-grade alkynyl,
B group: -ORa, -SRa, OH formed into - prodrug, the -O-low-grade alkylene ORa, the -O-low-grade alkylene O-low-grade alkylene ORa, the -O-low-grade alkylene NRaRb, the -O-low-grade alkylene O-low-grade alkylene NRaRb
The -O-low-grade alkylene NRc-low-grade alkylene NRaRb, -OCO-NRa
The Rb, -SORa, -SO2Ra, -SO2NRaRb, -NRa-SO2Rb, -NRaRb, and -NRc-low-grade alkylene NRaRb, - N (- low-grade alkylene NRaRb)
2, -RinD, -NO2, -CN, - halogen, -CO2Ra, -CONRaRb
-CONRa-O-Rb, -NRa-CORb, -NRa-CO-NRbRc, -OCORa, and -CO-Ra,
- Low-grade Al who may have the prodrug-ized OH:-OCO-substituent
Low-grade alkenylene C which may have Killen COOR and a -OCO-substituent
Aryl, -OCO low-grade ARUKIRE which may have OOR and a -OCO-substituent
The **- O-low-grade alkylene COOR, -OCO-CO-R, and a -OCO-substituent
The low-grade alkylene COOR which may have the low-grade alkyl and -OSO2-substituent which you may have, -O-lid RIJIRU, the 5-methyl 1, 3-dioxo ****-
2-****- 4-****- methyloxy,
R: H or low-grade alkyl,
Ra, Rb, and Rc: It is the same or different and they are -H, - low-grade alkyl, the - low-grade alkylene RinD, or -RinD,
RinD: - (5 which may have one or more substituents chosen from C group, or 7 member saturation heterocycle), - (Cycloalkyl which may have one or more substituents chosen from C group) - (Cyclo ARUKENIRU which may have one or more substituents chosen from C group) - (aryl which may have one or more substituents chosen from C group), or - (heteroaryl which may have one or more substituents chosen from C group),
C group: - low-grade alkyl, - halogen, - halogeno low-grade alkyl, -ORa1 -
O-low-grade alkylene ORa1, -SRa1, -NRa1Rb1, -NO2, -CN, -CO2Ra1, -CO-NRa1Rb1, -CORa1, - NRa1-CORb1, -SO2N
Ra1Rb1, - low-grade alkylene NRa1Rb1, - aryl, - low-grade Al ******-**
A reel and -OCO-Ra1,
Ra1 and Rb1: It is the same or different and they are -H or - low-grade alkyl,

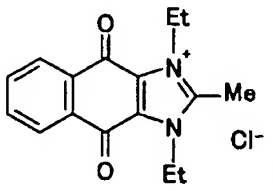
R3:-H -- or (- halogen, -ORa1, -SRa1, -NRa1Rb1, -NO2 **)
the low-grade alkylene of carbon numbers 2 to 5 which the low-grade alkyl which may have one or more substituents chosen from **-CN, or R2 and R3 are united, and may be interrupted for O, S, or NR4 (R4:-H or - low-grade alkyl) may be formed -- and
A ring: Benzene ring which may have one or more substituents chosen from C group.
[Claim 4] The condensation imidazole derivative shown with a following general formula (III), or its salt.
[Formula 3]



(The sign in a formula shows a following meaning.)
R1: -O-low-grade alkyl, the -O-low-grade alkylene RinD, -O-RinD, -S-low-grade alkyl, the -S-low-grade alkylene RinD, -S-RinD,
- The O-low-grade alkylene ORa, the -O-low-grade alkylene O-low-grade alkylene ORa, - NRa-CO-low-grade alkyl, the -NRa-CO-low-grade alkylene RinD, -NRa-CO-RinD, -(5 which may have one or more substituents chosen from C group, or 7 member saturation heterocycle)- (one or more substitution chosen from C group)
Cycloalkyl and - (one or more ** chosen from C group) which may have a group
Low-grade alkyl which has one or more substituents chosen from the heteroaryl which may have a ** machine,
Ra, Rb, and Rc: It is the same or different and they are -H, - low-grade alkyl, the - low-grade alkylene RinD, or -RinD,
RinD: - (5 which may have one or more substituents chosen from C group, or 7 member saturation heterocycle), - (Cycloalkyl which may have one or more substituents chosen from C group) - (Cyclo ARUKENIRU which may have one or more substituents chosen from C group) - (aryl which may have one or more substituents chosen from C group), or - (heteroaryl which may have one or more substituents chosen from C group),
C group: - low-grade alkyl, - halogen, - halogeno low-grade alkyl, -ORa1 -
O-low-grade alkylene ORa1, -SRa1, -NRa1Rb1, -NO2, -CN, -CO2Ra1, -CO-NRa1Rb1, -CORa1, -NRa1-CORb1, -SO2N
Ra1Rb1, - low-grade alkylene NRa1Rb1, - aryl, - low-grade Al ******-**
A reel and -OCO-Ra1,
Ra1 and Rb1: It is the same or different and they are -H or - low-grade alkyl,
R3:-H -- or (- halogen, -ORa1, -SRa1, -NRa1Rb1, -NO2 **)
the low-grade alkyl which may have one or more substituents chosen from **-CN -- and
A ring: Benzene ring which may have one or more substituents chosen from C group.
[Detailed Description of the Invention]
[0001]
[Field of the Invention]
This invention relates to medicine, a new condensation imidazolium inductor especially useful for the therapy of cancer, and its new manufacture intermediate product compound.
[0002]
[Description of the Prior Art]
As the aryl ring or heteroaryl ring which has antitumor activity conventionally, and the condensed imidazolium inductor, 4 of bottom type and 9-dioxo [2 and 3-naphth d] imidazolium compound (KP-1, KP-3 grade) is [only being indicated by Khim.Pharm.Zh., 32 (6), and 10-11 (1998) and].
[Formula 4]



(KP-1)



(KP-3)

(Et shows ethyl among a formula and Me shows methyl, respectively.) the following -- the same .
J. Med.Chem., 7 (3), and 362-364 (1964), In the general formula (I) of after-mentioned this invention, both R1 and R2 are low-grade alkyl, or one side is - low-grade alkylene (aryl which may have one or more substituents), and another side is -CH3. - (CH2)
3CH3, the compound which is - phenyl group, or one side is - low-grade alkylene CO- (aryl which may have one or more substituents), and -CH2CH(CH3)2 or -(CH2) 3CH3, and the indication of a compound that comes out and has a certain antimicrobial action have another side. However, there is no indication about an anticancer operation.

[0003]

Furthermore, in [J.Org.Chem.USSR, 1, 1479-85 (1965), JP,H3-258765,A, JP,H6-59371,A, etc.] the general formula (I) of after-mentioned this invention, 4 and 9-dioxo [2 and 3-naphth d] imidazolium inductor both R1 and whose R2 are low-grade alkyl groups is indicated. However, there is no indication about the medicine use of these compounds.

[0004]

The indication of isoquinoline 5 useful as an herbicide and 8-dione inductor has useful as herbicide 1, 4-dihydro1, and 4-dioxo naphthalene inductor in the British Patent No. 1314881 gazette at Japanese patent JP,S54-25085,B, respectively. Moreover, some 1, 4-dihydro1, and 4-dioxo naphthalene inductors are Zh. Org.Khim. and 22 (8), 1736-42 J.Gen.Chem.USSR, 36, and 649-652 (1966), (1986) And it is well-known by a reagent catalog [Sigma Aldrich Library of Rare Chemicals Structure Index, with update (Aldrich Chemical Company, Inc.), etc.]. However, about the medicine use of these compounds, there is all no indication.

WO 97/No. 30022 gazette, J.Med.Chem.39, 1447-1451 (1996) and J.Med.Chem., 7 (3), and 362-364 (1964) have the indication of an aryl ring and the condensed imidazole derivative.

[0005]

[Problem(s) to be Solved by the Invention]

It has a good anticancer operation and is still anxious for the invention of the anticancer agent which is moreover low toxicity.

[0006]

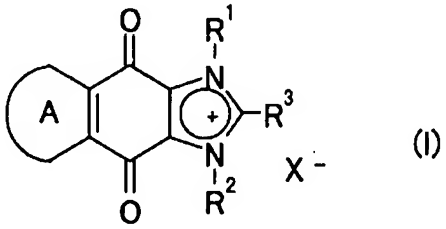
[Means for Solving the Problem]

It is characterized by replacing the 1st place and/or the 3rd place by the alkyl group which has a substituent, as a result of this invention person's etc. taking lessons from an anticancer agent with few side reactions and inquiring wholeheartedly. While a new aryl ring or a heteroaryl ring, and the condensed imidazolium inductor have good antitumor activity, it is low toxicity, and it found out that it could become the large anticancer agent of a safety margin. Moreover, the 2-acylamino 3-amino 1 useful as these manufacture intermediate products, 4-quinone derivative, and a condensation imidazole derivative are found out. Furthermore, the 2-acylamino 3-amino 1 and the 4-quinone derivative itself which is this manufacture intermediate product also carry out the knowledge of having good antitumor action by low toxicity, and completes this invention.

[0007]

That is, this invention relates to the condensation imidazolium inductor shown with a following general formula (I).

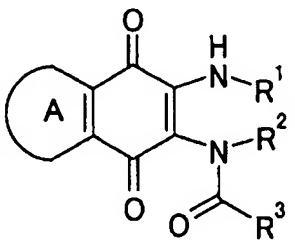
[Formula 5]



(I)

(The sign in a formula shows a following meaning.)
R1 and R2: Either is -O-low-grade alkyl and a -O-low-grade alkylene.
RinD, -O-RinD, -S-low-grade alkyl, the -S-low-grade alkylene Ri
The nD, -S-RinD, and -O-low-grade alkylene ORa, the -O-low-grade alkylene O-low-grade alkylene ORa, - NRa-low-grade alkyl, the -NRa-low-grade alkylene RinD, -NRa-RinD, - NRa-CO-low-grade alkyl, the -NRa-CO-low-grade alkylene RinD, -NRa-CO-RinD, -(5 which may have one or more substituents chosen from C group, or 7 member saturation heterocycle)- (C)
Cycloalkyl and - which may have one or more substituents chosen from a group
the heteroaryl which may have one or more substituents chosen from C group -- from
It is low-grade alkyl which has one or more substituents chosen from ****.;

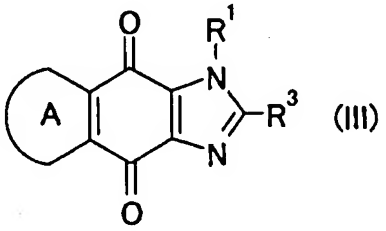
Another side - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) They are - (low-grade alkynyl which has one or more substituents chosen from B group), -RinD, - low-grade alkyl, - low-grade ARUKENIRU, or - low-grade alkynyl,
B group : -ORa, -SRa, OH formed into - prodrug, the -O-low-grade alkylene ORa, - The O-low-grade alkylene O-low-grade alkylene ORa, the -O-low-grade alkylene NRaRb, the -O-low-grade alkylene O-low-grade alkylene NRaRb, the -O-low-grade alkylene NRc-low-grade alkylene NRaRb, -OCO-NRaR b, -SORa, -SO2Ra, -SO2NRaRb, -NRa-SO2Rb, -NRaRb
The -NRc-low-grade alkylene NRaRb, -N(- low-grade alkylene NRaRb)2
-RinD, -NO2, -CN, - halogen, -CO2Ra, -COO-, -CONRaRb, -CONRa-O-Rb, -NRa-CORb, -NRa-CO-NRbR
c, -OCORa, and -CO-Ra,
- Low-grade Al who may have the prodrug-ized OH:-OCO-substituent
Low-grade alkenylene C which may have Killen COOR and a -OCO-substituent
Aryl, -OCO low-grade ARUKIRE which may have OOR and a -OCO-substituent
The **- O-low-grade alkylene COOR, -OCO-CO-R, and a -OCO-substituent
The low-grade alkylene COOR which may have the low-grade alkyl and -OSO2-substituent which you may have, -O-lid RIJIRU, the 5-methyl 1, 3-dioxo ****-
2-****- 4-****- methyloxy,
R: H or low-grade alkyl,
Ra, Rb, and Rc: It is the same or different and they are -H, - low-grade alkyl, the - low-grade alkylene RinD, or -RinD,
RinD: - (5 which may have one or more substituents chosen from C group, or 7 member saturation heterocycle), - (Cycloalkyl which may have one or more substituents chosen from C group) - (Cyclo ARUKENIRU which may have one or more substituents chosen from C group) - (aryl which may have one or more substituents chosen from C group), or - (heteroaryl which may have one or more substituents chosen from C group),
C group: - low-grade alkyl, - halogen, - halogeno low-grade alkyl, -ORal -
O-low-grade alkylene ORal, -SRal, -NRalRbl, -NO2, -CN, -CO2Ral, -CO-NRalRbl, -CORal, -NRal-CORbl, -SO2N
RalRbl, - low-grade alkylene NRalRbl, - aryl, - low-grade Al ******-**
A reel and -OCO-Ral,
Ral and Rbl: It is the same or different and they are -H or - low-grade alkyl,
R3:-H -- or (- halogen, -ORal, -SRal, -NRalRbl, -NO2 **)
You may form the low-grade alkylene of carbon numbers 2 to 5 which the low-grade alkyl which may have one or more substituents chosen from **-CN, or R2 and R3 are united, and may be interrupted for O, S, or NR4 (R4:-H or - low-grade alkyl),
A ring: -- benzene ring which may have one or more substituents chosen from C group -- and
X-: When counter anion, however substituent-COO- of B group and imidazolium ion form inner salt, X- does not exist.
However, both R1 and R2 remove the compound which is an ethoxyethyl machine. the following -- the same .
[0008]
Moreover, this invention is the manufacture intermediate product of the above-mentioned general formula (I), and, also in itself, relates to the 2-acylamino 3-amino 1 and 4-quinone derivative which are shown with the following general formula (II) which has a good anticancer operation, or its salt.
[Formula 6]



(II)

(The sign in a formula shows a following meaning.)
R1 and R2: Either is -O-low-grade alkyl and a -O-low-grade alkylene.
RinD, -O-RinD, -S-low-grade alkyl, the -S-low-grade alkylene Ri
The nD, -S-RinD, and -O-low-grade alkylene ORa, the -O-low-grade alkylene O-low-grade alkylene ORa, - NRa-low-grade alkyl, the -NRa-low-grade alkylene RinD, -NRa-RinD, - NRa-CO-low-grade

alkyl, the -NRa-CO-low-grade alkylene RinD, -NRa-CO-RinD, -(5 which may have one or more substituents chosen from C group, or 7 member saturation heterocycle)- (C)
Cycloalkyl and - which may have one or more substituents chosen from a group
From heteroaryl to ** which may have one or more substituents chosen from C group
It is low-grade alkyl which has one or more substituents **(ed).;
Another side - (low-grade alkyl which has one or more substituents chosen from B group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B group) They are - (low-grade alkynyl which has one or more substituents chosen from B group), -RinD, - low-grade alkyl, - low-grade ARUKENIRU, or - low-grade alkynyl,
B group: -ORa, -SRa, OH formed into - prodrug, the -O-low-grade alkylene ORa, the -O-low-grade alkylene O-low-grade alkylene ORa, the -O-low-grade alkylene NRaRb, the -O-low-grade alkylene O-low-grade alkylene NRaRb
The -O-low-grade alkylene NRc-low-grade alkylene NRaRb, -OCO-NRa
The Rb, -SORa, -SO2Ra, -SO2NRaRb, -NRa-SO2Rb, -NRaRb, and -NRc-low-grade alkylene NRaRb, -N (- low-grade alkylene NRaRb)
2, -RinD, -NO2, -CN, - halogen, -CO2Ra, -CONRaRb
-CONRa-O-Rb, -NRa-CORb, -NRa-CO-NRbRc, -OCORa, and -CO-Ra,
- Low-grade Al who may have the prodrug-ized OH:-OCO-substituent
Low-grade alkenylene C which may have Killen COOR and a -OCO-substituent
Aryl, -OCO low-grade ARUKIRE which may have OOR and a -OCO-substituent
The **- O-low-grade alkylene COOR, -OCO-CO-R, and a -OCO-substituent
The low-grade alkylene COOR which may have the low-grade alkyl and -OSO2-substituent which you may have, -O-lid RIJIRU, the 5-methyl 1, 3-dioxo ****-
2-****- 4-****- methyloxy,
R: H or low-grade alkyl,
Ra, Rb, and Rc: It is the same or different and they are -H, - low-grade alkyl, the - low-grade alkylene RinD, or -RinD,
RinD: - (5 which may have one or more substituents chosen from C group, or 7 member saturation heterocycle), - (Cycloalkyl which may have one or more substituents chosen from C group) - (Cyclo ARUKENIRU which may have one or more substituents chosen from C group) - (aryl which may have one or more substituents chosen from C group), or - (heteroaryl which may have one or more substituents chosen from C group),
C group: - low-grade alkyl, - halogen, - halogeno low-grade alkyl, -ORa1, -O-low-grade alkylene ORa1, -SRa1, -NRa1Rb1, -NO2, -CN, -CO2Ra1, -CO-NRa1Rb1, -CORa1, -NRa1-CORb1, -SO2N
Ra1Rb1, - low-grade alkylene NRa1Rb1, - aryl, - low-grade Al ******-**
A reel and -OCO-Ra1,
Ra1 and Rb1: It is the same or different and they are -H or - low-grade alkyl,
R3:-H -- or (- halogen, -ORa1, -SRa1, -NRa1Rb1, -NO2 **)
the low-grade alkylene of carbon numbers 2 to 5 which the low-grade alkyl which may have one or more substituents chosen from **-CN, or R2 and R3 are united, and may be interrupted for O, S, or NR4 (R4:-H or - low-grade alkyl) may be formed -- and
A ring: Benzene ring which may have one or more substituents chosen from C group. the following -- the same .
[0009]
[0010]
[0011]
Furthermore, this invention relates to the condensation imidazole derivative which is a new manufacture intermediate product of the above-mentioned general formula (I) and which is shown with a following general formula (III), or its salt.
[Formula 7]



(The sign in a formula shows a following meaning.)

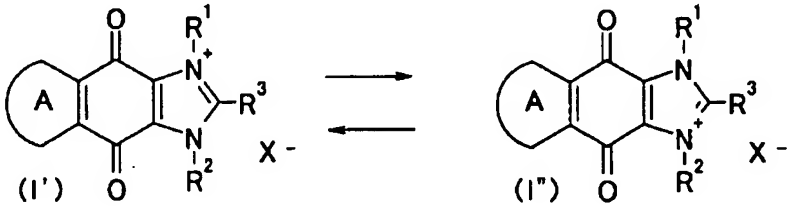
R1: -O-low-grade alkyl, the -O-low-grade alkylene RinD, -O-RinD, -S-low-grade alkyl, the -S-low-grade alkylene RinD, -S-RinD,
- The O-low-grade alkylene ORa, the -O-low-grade alkylene O-low-grade alkylene ORa, - NRa-CO-low-grade alkyl, the -NRa-CO-low-grade alkylene RinD, -NRa-CO-RinD, -(5 which may have one or more substituents chosen from C group, or 7 member saturation heterocycle)- (one or more substitution chosen from C group)
Cycloalkyl and - (one or more ** chosen from C group) which may have a group
Low-grade alkyl which has one or more substituents chosen from the heteroaryl which may have a ** machine,
Ra, Rb, and Rc: It is the same or different and they are -H, - low-grade alkyl, the - low-grade alkylene RinD, or -RinD,
RinD: - (5 which may have one or more substituents chosen from C group, or 7 member saturation heterocycle), - (Cycloalkyl which may have one or more substituents chosen from C group) - (Cyclo ARUKENIRU which may have one or more substituents chosen from C group) - (aryl which may have one or more substituents chosen from C group), or - (heteroaryl which may have one or more substituents chosen from C group),
C group: - low-grade alkyl, - halogen, - halogeno low-grade alkyl, -ORa1 -
O-low-grade alkylene ORa1, -SRa1, -NRa1Rb1, -NO2, -CN, -CO2Ra1, -CO-NRa1Rb1, -CORa1, - NRa1-CORb1, -SO2N
Ra1Rb1, - low-grade alkylene NRa1Rb1, - aryl, - low-grade Al ******-**
A reel and -OCO-Ra1,
Ra1 and Rb1: It is the same or different and they are -H or - low-grade alkyl,
R3:-H -- or (- halogen, -ORa1, -SRa1, -NRa1Rb1, -NO2 **)
the low-grade alkyl which may have one or more substituents chosen from **-CN -- and
A ring: Benzene ring which may have one or more substituents chosen from C group. the following -- the same .
[0012]
[Embodiment of the Invention]
A general formula (I) and the compound which (II) Reaches (III) are explained further.
The word "low-grade" Becoming means the hydrocarbon chain of the shape of a straight chain of 1-6 carbon numbers, or the letter of branching among this Description. As "low-grade alkyl", it is the alkyl group of 1 to 4 carbon numbers preferably, and they are methyl, ethyl, n-propyl, isopropyl, n-butyl, and an isobutyl machine especially preferably. As "low-grade ARUKENIRU", they are vinyl, an allyl compound, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, and 3-butenyl group preferably. As "low-grade alkynyl", they are ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, and 1-methyl 2-propynyl group preferably. Moreover, as a "low-grade alkylene", it is methylene, ethylene, trimethylene and 2, and 2-dimethyl trimethylene machine preferably.
As "aryl", an aromatic hydrocarbon ring machine is meant, and the aryl group of 6 to 14 carbon numbers is desirable, and are a phenyl, naphthyl, and a fluorenyl group preferably.

[0013]
5 which contains as "heteroaryl" 1 to 4 hetero atoms chosen from N, S, and O or 6 member monocycle heteroaryl group, and these are benzene-ring or 5 to 6 member monocycle heteroaryl and condensed 2 ring type heteroaryl group, and may be saturated partially. Moreover, when N atom is included, you may form N-oxide. Here as 5 to 6 member monocycle heteroaryl A furil, thienyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, Iso thiazolyl, oxazolyl, iso oxazolyl, oxadiazolyl, Thiadiazolyl, triazoryl, tetra-ZORIRU, pyridyl, pyrimidinyl, pilus DAJINIRU, pyrazinyl ones, and a thoriadinyl group are desirable, and as 2 ring type heteroaryl Benzofuranyl one, benzothienyl, benzothiadiazolyl, benzothiazolyl, Benzoxazolyl, benzooxadiazolyl, benzoimidazolyl, India Lil, iso India Lil, indazolyl, quinolyl, iso quinolyl, SHINNORINIRU, chinae-cortex ZORINIRU, KINOKISARINIRU, benzodioxolyl, in DORIJINIRU, and an imidazo pyridyl machine are desirable. As partial saturation heteroaryl, a 1, 2, 3, and 4-tetrahydro quinolyl machine etc. is mentioned. Furthermore, preferably, it is a furil, thienyl, imidazolyl, pyridyl, pyrazinyl one, pyrimidinyl, pilus DAJINIRU, India Lil, benzoimidazolyl, benzodioxo nil, and a quinolyl machine, and they are pyridyl, pyrazinyl one, and a pyrimidinyl group especially preferably.
[0014]
As "cycloalkyl", it is the cycloalkyl machine of 3-10 carbon numbers preferably, and they are cyclo propyl, cyclopentyl, cyclohexyl, and an adamanthyl machine especially preferably. As "cyclo ARUKENIRU", it is the cyclo alkenyl group of 3-8 carbon numbers preferably, and they are cyclo pentenyl and a cyclohexenyl group especially preferably.
If it is anion pharmaceutically permitted as counter anion of imidazolium ion as "counter anion", there will be no restriction in particular and preferably a halogen ion and an organic-sulfonic-acid ion (for

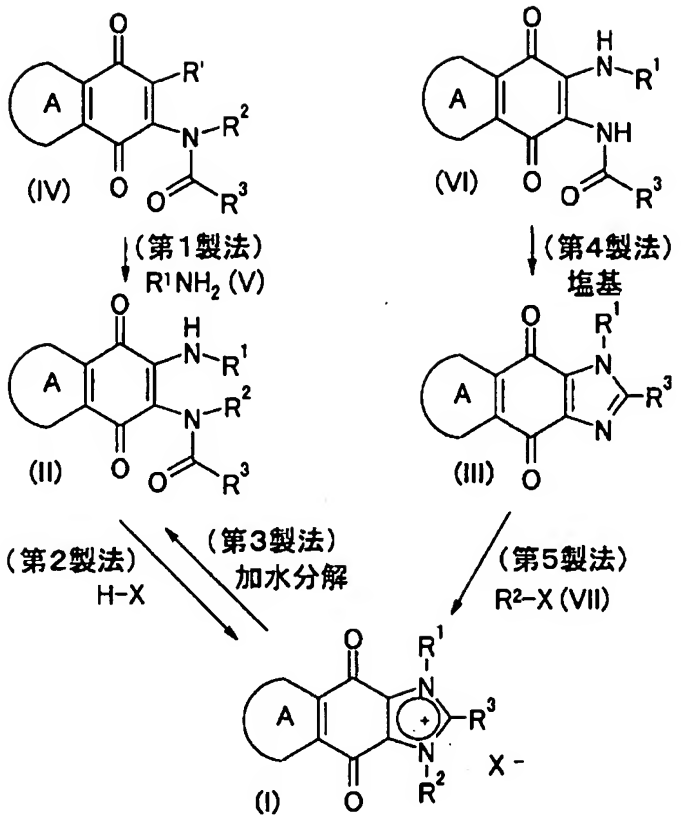
example, a methansulfonic acid ion --) Anion univalent [, such as acetate ions, such as an ethane-sulfonic-acid ion, a benzenesulfonic acid ion, and a toluenesulfonic acid ion, trifluoro acetate ion, carbonate ion, and sulfate ion,] or divalent is mentioned, and it is a halogen ion especially preferably. As "halogen", F, Cl, Br, and I atom are mentioned, and they are these ions as a "halogen ion." As "halogeno low-grade alkyl", said halogen is said low-grade alkyl replaced one or more, and is -CF3 preferably.
"5 to 7 member saturation heterocycle" is 5 containing 1 to 4 hetero atoms chosen from N, S, and O, 7 member monocycle saturation heterocycle, or its bridge ring. They are tetrahydropyranyl, tetrahydrofuranyl one, pyrrolidinyl, piperazinyl one, AZEPANIRU, JIAZEPANIRU, quinuclidinyl, piperidyl, and a mole HORINIRU machine preferably.
[0015]
"OH formed into - prodrug" is the group in which the reversible prodrug inductor restored to a parent compound (hydroxy compound of a yuan) in the living body was formed -- for example, Prog. They are Med.5 and the group indicated to 2157-2161 (1985). the low-grade alkylene COOR (R shows H or low-grade alkyl --) which may have a -OCO-substituent preferably The low-grade alkenylene COOR which may have a -OCO-substituent like the following - The aryl, the -OCO low-grade alkylene O-low-grade alkylene COOR which may have an OCO-substituent - The low-grade alkylene COOR which may have the low-grade alkyl and -OSO2-substituent which may have OCO-CO-R and a -OCO-substituent, -O-lid RIJIRU, the 5-methyl 1, 3-dioxo ****- 2-****- 4-****- methyloxy, etc. are mentioned.
[0016]
A still more desirable group among the substituent of said C group - low-grade alkyl, - halogen, - Halogeno low-grade alkyl, -OH, -O-low-grade alkyl, the -O-low-grade alkylene OH, - They are O-low-grade alkylene O-low-grade alkyl, - low-grade alkylene NH2, -NH2, -NH-low-grade alkyl, -N(low-grade alkyl)2, and -CO2H, -CO2-low-grade alkyl, -CO-NH2, -SO2-NH2, -NO2, and -CN.
As a substituent in "benzene ring which may have one or more substituents" in A ring, the group of said C group is mentioned and a still more desirable group is the same as that of the above. It is -NO2 especially preferably.
[0017]
As a substituent in "the low-grade alkyl which may have one or more substituents" of R3, they are - halogen, -ORa, -SRa, -NRaRb, -NO2, and -CN.
In addition, in said B group, the group Ra, Rb, and whose Rc are -H or - low-grade alkyl is more desirable as a group shown using Ra, Rb, and Rc.
["forming the low-grade alkylene of carbon numbers 2 to 5 which R2 and R3 are united and may be interrupted for O, S, or NR4 (R4:-H or - low-grade alkyl)"] The low-grade alkylene chain which may be interrupted for O, S, or NR4 which R2 and R3 form (preferably) - (CH2) Mean the adjoining N and adjoining C atom being united with 4-, -(CH2)2OCH2-, and -(CH2) 2N(Me) CH2-, and forming 4 to 7 member heterocycle.
[0018]
In this invention compound (I) or (II), it is a desirable compound,
(1) Either [at least] R1 or R2 are -ORa and the -O-low-grade alkylene ORa.
The -O-low-grade alkylene O-low-grade alkylene ORa, - (5 which may have one or more substituents chosen from C group, or 7 member saturation heterocycle), - (Aryl which may have one or more substituents chosen from C group) And the compound which is low-grade alkyl which has one or more substituents chosen from the group which consists of - (heteroaryl which may have one or more substituents chosen from C group),
(2) Either [at least] R1 or R2 may have one or more substituents chosen from C group. The compound which is low-grade alkyl replaced by the heteroaryl group chosen from (a furil, thienyl, imidazolyl, pyridyl, pyrazinyl ones, pyrimidinyl, pilus DAJINIRU, India Lil, benzoimidazolyl, benzodioxo nil, and a quinolyl machine),
(3) Either R1 or R2 are low-grade alkyl replaced by -O-low-grade alkyl. Another side -O-low-grade alkylene O-low-grade alkyl and -O-low-grade alkylene O-low-grade alkylene O-low-grade alkyl, - (Aryl which may have one or more substituents chosen from C group) The compound which is low-grade alkyl which has one substituent chosen from the group which consists of - (heteroaryl which may have one or more substituents chosen from C group), and -O-low-grade alkyl,
(4) either [at least] R1 or R2 - (you may have one or more substituents chosen from C group --) The compound which is low-grade alkyl which has one substituent chosen from the group which consists of heteroaryl, -O-low-grade alkylene O-low-grade alkyl, and -O-low-grade alkyl which are chosen from pyridyl, pyrazinyl ones, and a pyrimidinyl group,
(5) The compound whose R3 is a methyl group,
(6) the compound which is benzene ring by which A ring may be replaced by -NO2 -- or
(7) X- is the compound which is a halogen ion.
[0019]

Moreover, desirable compound with the another this invention compound (I) is any 1 of R1 and R2.
Directions are -O-low-grade alkyl, the -O-low-grade alkylene RinD, and -O-RinD.
-S-low-grade alkyl, the -S-low-grade alkylene RinD, -S-RinD -
The O-low-grade alkylene ORa, the -O-low-grade alkylene O-low-grade alkylene ORa, -NRa-low-grade alkyl, the -NRa-low-grade alkylene RinD, -NRa -
RinD, -NRa-CO-low-grade alkyl, the -NRa-CO-low-grade alkylene R
inD, -NRa-CO-RinD, -(5 which may have one or more substituents chosen from C' group, or 7 member saturation heterocycle)- (1 or more [it is chosen from C' group])
Cycloalkyl and - (1 chosen from C' group) which may have ********
1 chosen from the group which consists of heteroaryl which may have the above substituent
It is low-grade alkyl which has the above substituent.;
Another side - (low-grade alkyl which has one or more substituents chosen from B' group), - (Low-grade ARUKENIRU which has one or more substituents chosen from B' group) - (Low-grade alkynyl which has one or more substituents chosen from B' group) - (Cycloalkyl which may have one or more substituents chosen from C' group) - (5 or 6 member monocycle heteroaryl which may have one or more substituents chosen from C' group) - (Aryl which may have one or more substituents chosen from C' group) - (5 or 7 member saturation heterocycle which may have one or more substituents chosen from C' group) - A low-grade alkylene (aryl which may have one or more substituents chosen from C' group), - Low-grade alkylene CO- (aryl which may have one or more substituents chosen from C' group), - It is low-grade alkyl and - low-grade ARUKENIRU or - low-grade alkynyl, and a;B' group is -ORa, -SRa, OH [that was formed into - prodrug], -O-low-grade alkylene RinD, -SORa, -SO2Ra, and -SO2.
The NRaRb, NRa-SO2Rb, -NRaRb, and -NRc-low-grade alkylene RinD, -N(- low-grade alkylene RinD) 2, the -NRc-low-grade alkylene NRaRb
- N(low-grade alkylene NRaRb)2, - (5 which may have one or more substituents chosen from C' group, or 7 member saturation heterocycle), - (5 which may have one or more substituents chosen from C' group, or 6 member monocycle heteroaryl) - Cycloalkyl, the -S-low-grade alkylene RinD, -NO2, -CN, - CO2Ra, -CONRaRb, -NRa-CORb, -OCORa, Are -CO-low-grade alkyl and -CO- (5 which may have one or more substituents chosen from C' group, or 6 member monocycle heteroaryl), and;Ra, Rb and Rc are the same or different, are -H, - low-grade alkyl, or -RinD, and;RinD - (5 which may have one or more substituents chosen from C' group, or 7 member saturation heterocycle), - (Aryl which may have one or more substituents chosen from C' group) or -- it is - (5 which may have one or more substituents chosen from C' group, or 6 member monocycle heteroaryl) -- a;C' group - low-grade alkyl, - halogen, -ORa, - SRa, -NRaRb, and -NO
Are 2, -CN, -CO2Ra, -CO-NRaRb, -CORa, -NRa-CORb, and -OCO-Ra, and;R3 are -H or - low-grade alkyl, and [;A ring] - It is the condensation imidazolium inductor; and whose X- it is benzene ring which may have the substituent chosen from the group which consists of low-grade alkyl and -ORa, - NRaRb, -CN, - halogen, and -NO2, and are counter anion.
[0020]
[especially a desirable compound] among this invention compound (I) The 1-[(6-chloro 3-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, 1, the 2-dimethyl 4, 9-dioxo 3-[(2-tetrahydrofuranyl) methyl]-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, 1, the 3-bis(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 1-(2-pyrazinyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-[3-(1H-4-imidazolyl) propyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, 3-(2-methoxy ethyl)-2-methyl 1-[(5-methyl 2-pyrazinyl) methyl]-4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 2-methyl 4, 9-dioxo 1, 3-bis(2-pyrazinyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-[2-(2-methoxyethoxy) ethyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-{2-[2-(2-methoxyethoxy) ethoxy] ethyl}-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 3-(3-pyridyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 1-(2-pyridyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 1-(4-pyridyl methyl)-4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-[(2-chloro 3-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-[(2-hydroxy 4-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 3-(2-methoxy ethyl)-1-[(6-methoxy 3-pyridyl) methyl]-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-[(2-chloro 4-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-(4-chloro benzyl)-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, The 1-(4-fluoro benzyl)-3-(2-methoxy ethyl)-2-methyl 4, 9-dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU, It is the salt of 1, 3-bis(2-methoxy ethyl)-2-methyl 5-nitroglycerine 4, 9-

dioxo 4, 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU or these tautomers, and a halogen ion.
[0021]
The compound (I) of this invention has the tautomer shown by the bottom formula depended on delocalization of a cation, and the thing which these isomers separated, or a mixture is included by this invention. Therefore, the compound written as a 1H-imidazole 3-IUMU inductor includes the mixture of the 3H-imidazole 1-IUMU inductor which is a tautomer, and both isomers among this Description. In addition, when a compound (I) has substituent-COO- and forms imidazolium ion and inner salt, X- does not exist.
[Formula 8]



[0022]
this invention compound (I) may form a salt depending on the kind of substituent in addition to a salt with said counter anion, and these salts are also included by this invention. Moreover, a salt may be formed depending on this invention compound (II) or (III) the kind of substituent, and these salts are also included by this invention. If it is the salt pharmaceutically permitted as a salt here, there will be no restriction in particular, but as acid addition salt Specifically Inorganic acids, such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid, formic acid, acetic acid, a propionic acid, an oxalic acid, malonic acid, succinic acid, a fumaric acid, a maleic acid, lactic acid, a malic acid, tartaric acid, citric acid, methansulfonic acid, ethane sulfonic acid, aspartic acid, It is mentioned by acid addition salt with organic acids, such as glutamic acid, etc., and as a salt with a base Salts, ammonium salt, etc. with an organic base, such as the inorganic base containing metals, such as sodium, potassium, magnesium, calcium, and an aluminium, or monomethylamine, ethylamine, ethanolamine, lysine, and ornithine, are mentioned.
Although a geometrical isomer and a tautomer may exist depending on the kind of this invention compound (I), (II), or (III) substituent, the thing which these isomers separated, or a mixture is included by this invention. Furthermore, this invention compound may have an asymmetric carbon atom, and the isomer based on an asymmetric carbon atom may exist. This invention includes the mixture and the thing which isolated of these optical isomers. Moreover, this invention compound may form N-oxide depending on the kind of substituent, and these N-oxide objects are also included by this invention. furthermore, this invention -- this invention compound (I) and (II) -- or (III) also includes the substance of various kinds of hydrates, solvate, and crystal polymorphism. [0023]
(Manufacturing method)
A method this invention compound (I), (II), and (III) given in literature For example, J.Org.Chem. USSR, 1, and 1479-85 (1965), J. With the application of a well-known method, it can manufacture easily to a person skilled in the art, using the method indicated to Med.Chem., 7 (3), 362-364 (1964), JP, H3-258765,A, etc., and the same method.
In addition, depending on the kind of functional group, a raw material or a blocking group suitable in the stage of an intermediate product, i.e., transpose to the group which can be converted into the functional group concerned easily, may be effective on manufacture technology in the functional group concerned. The appropriate back can remove a blocking group if needed, and a desired compound can be obtained. As such a functional group, for example, an amino group, a hydroxyl group, Can mention a carboxyl group etc. and as those blocking groups The blocking group of ** (Greene), for example, Green, and the Wuts (Wuts) work, "Protective Groups in Organic Synthesis", and the 2nd-edition description can be mentioned, and what is necessary is just to use these suitably according to a reaction condition.
A typical production method is explained below.
[0024]
[Formula 9]



(Inside of formula and R' means hydrogen, methoxy or a halogen group, and the acids (preferably hydrogen fluoride, hydrogen chloride, a hydrogen bromide, hydrogen iodide, methansulfonic acid, ethane sulfonic acid, etc.) with which H-X forms anion.) the following -- the same .

[0025]

The 1st process

this invention compound (II) can be manufactured by making amines (V) react to a compound (IV) with a conventional method. A reaction, for example Chem.Pharm.Bull., 44 (6), 1181-1187 Tetrahedron. Lett., 39 (42), (1996) 7677-7678 (1998) Etc. -- [it Can Manufacture with the application of the Method of Description, and] the compound (IV) of the inside of suitable inert solvents (for example, benzene etc.), and a reaction equivalent amount, and (V) -- again -- yes -- using inorganic bases (potassium carbonate etc.) or organic bases suitable as an acid acceptor (triethylamine etc.) if needed using an excessive quantity of gaps or one side -- ordinary temperature or warming -- it is advantageous to carry out in the bottom.

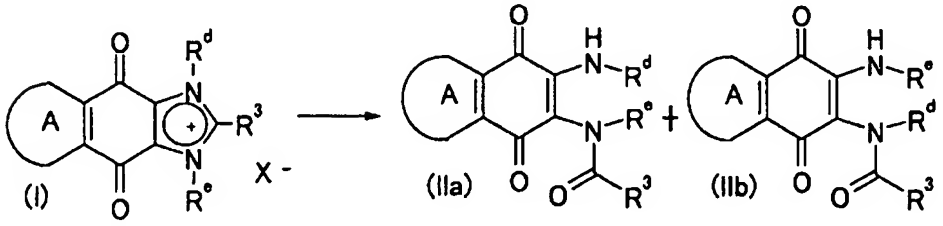
The 2nd process

With a conventional method, this invention compound (I) can manufacture this invention compound (II), cyclization and when the fourth class chlorinates. being able to perform a reaction with the application of the method of J.Org.Chem.USSR, 1, and given (1965) in 1479-85, for example, and using a reaction equivalent amount or an excessive quantity of acids among suitable inert solvents (for example, alcoholic solvent etc.) -- ordinary temperature or warming -- it is advantageous to carry out in the bottom.

[0026]

The 3rd process

[Formula 10]



(Rd and Re show among a formula the arbitrary groups defined as R1 and R2.)

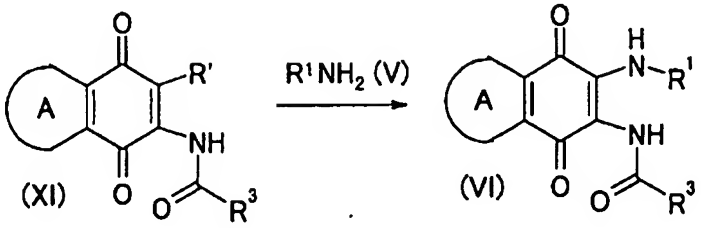
hydrolyzing this invention compound (I) with a conventional method -- two sorts of this invention

compounds (IIa) -- and (IIb) it can obtain. The obtained compound can be further given to the modification reaction of a well-known group, and can also be made into the manufacture intermediate product of the desired this invention compound (I).
the hydrolysis reaction can apply the method of a description to J.Med.Chem., 7 (3), 362-364 (1964), etc., and a reaction equivalent amount or an excessive quantity of bases are used for it among water and a suitable inert solvent (for example, ethanol etc.), for example -- ordinary temperature or warming -- it is advantageous to carry out in the bottom. As a base, lithium hydroxide, sodium hydroxide, a potassium hydroxide, sodium carbonate, potassium carbonate, etc. are mentioned here.
[0027]
The 4th process
this invention compound (III) can be manufactured in accordance with the method indicated to J.Med. Chem., 39 (7), 1447-1451 (1996), etc. from giving a compound (VI) to ring closure under existence of bases, such as sodium hydroxide.
The 5th process
this invention compound (I) can be manufactured by making a halide (VII) react to this invention compound (III), and considering it as the fourth class salt. Reactions are J.Med.Chem., 7 (3), and 362-364, for example. Can carry out with the application of the method of a description (1964), and preferably the compound (III) of the inside (for example, acetonitrile etc.) of a suitable inert solvent, and a reaction equivalent amount -- and (VII) -- again -- yes -- using an excessive quantity of gaps or one side -- ordinary temperature or warming -- it is [the bottom] advantageous to carry out under the flowing-back temperature of a solvent preferably.
Other manufacturing methods
this invention compound can also be manufactured by the modification reaction of the well-known substituent of versatility besides the above-mentioned process. For example, the compound which has the substituent including sulfonyl combination can be manufactured by oxidation reaction of a conventional method from the compound which has a sulfide bond or sulfinyl combination. Moreover, N-oxide inductor of the compound which has heteroaryl containing N atoms, such as a pyridyl machine, as a substituent can be manufactured by oxidation reaction of a conventional method. The compound which has the substituent containing carboxylic acid can be manufactured by the hydrolysis reaction of a conventional method from the compound which has ester or amide combination. The compound which has the substituent containing an amino alkyl group can be manufactured by the amination reaction of a conventional method from the compound which has a halogenation alkyl group. When it is this invention compound (II) and (III) educt, it can be considered as a salt by the salt formation reaction according to a conventional method by request.
[0028]
Synthesis of a raw material compound
Some raw material compounds of this invention compound are new molecular entities, and these compounds can be easily compounded like a well-known raw material compound using a well-known method to a person skilled in the art. A typical synthetic process is shown below.
Synthetic process 1
[Formula 11]

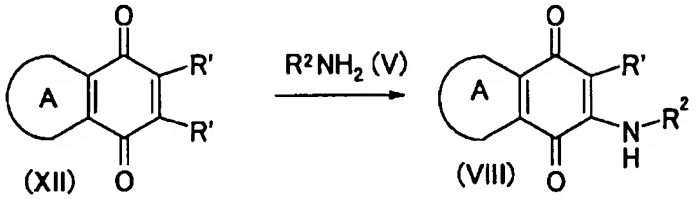
A compound (IV) meets the method indicated to J.Org.Chem.USSR, 1, 1479-85 (1965), etc., for example. A compound (VIII) can be manufactured by reactant carboxylic acid inductors, such as acid halide and an acid anhydride, and the acylation reaction of a conventional method made to react.
Synthetic process 2
[Formula 12]

(B1 shows among a formula the pyridine ring which may have a substituent.) the following -- the same . an aminomethyl pyridine inductor (X) -- the German patent No. 3726993 gazette (1989) etc. -- in

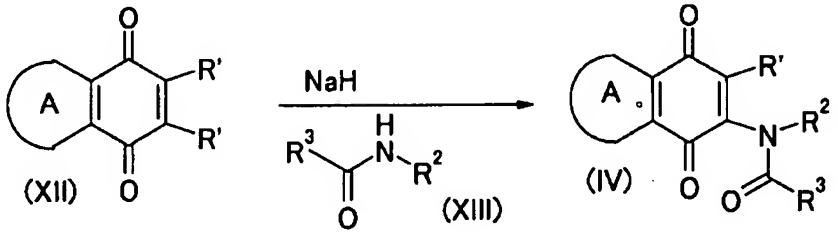
accordance with the indicated method, it can manufacture by reduction of a compound (IX).
[0029]
Synthetic process 3
[Formula 13]



A compound (VI) can be manufactured according to amination of a compound (XI) in accordance with the method indicated to J.Med.Chem., 39 (7), 1447-1451 (1996), etc.
Synthetic process 4
[Formula 14]



A compound (VIII) J.Het.Chem., 33 (1), 113-117 (1996) In accordance with the method indicated to Tetrahedron.Lett., 39 (42), 7677-7678 (1998), etc., it can manufacture according to amination of a compound (XII).
[0030]
Synthetic process 5
[Formula 15]



A compound (IV) can be manufactured by amidation of a compound (XII). The inside of an inert solvent with an appropriate reaction (for example, N, N dimethylformamide (DMF) etc.), the reaction equivalent amount after activating the compound (XIII) of a reaction equivalent amount using suitable inorganic bases (NaH etc.) or organic bases (NaOMe etc.), an excessive quantity of compounds (XII) and ordinary temperature, or warming -- it is advantageous to make it react in the bottom.
Thus, isolation and refining of the manufactured this invention compound are performed by being adapted in the usual chemical operation, such as extraction, concentration, distilling off, crystallization, filtration, recrystallization, and various chromatography.
Various kinds of isomers can isolate with a conventional method using the difference of the physicochemical character between isomers. For example, racemate can be led to an isomer pure on the [method [for example,] of leading to diastereomeric salt with common optical activity acids (tartaric acid etc.), and carrying out optical resolution] solid target by a general optical resolution method. Moreover, the mixture of a diastereomer is separable with fractional-crystallization-izing or chromatography, for example. Moreover, an optical activity compound can also be manufactured by using a suitable optical activity raw material.
[0031]
[Effect of the Invention]
The compound (I) of this invention and (II) have good cancer cell multiplication depressant action, and, moreover, are useful as a large anticancer agent of a safety margin at low toxicity. therefore, this invention compound -- cancer -- desirable -- all the solid carcinota and a lymphoma -- it has the multiplication depressant action of tumors, such as skin carcinoma, vesical cancer, a breast cancer, a uterine cancer, an ovarian cancer, a prostatic cancer, lung cancer, colon cancer, a pancreatic cancer, a

renal cancer, and gastric cancer, especially, and is useful for these therapies. Especially, in a cancer cell growth inhibition examination and the in vivo cancer growth inhibition examination using a mouse cancer-bearing model, it has the good antitumor activity exceeding the existing anticancer agent to two or more cancer types, and is expected as a treating agent of the cancer type which shows the existing anticancer agent tolerance.

[0032]

The effect of this invention compound was checked by the following examinations.

Example 1 of an examination Cancer cell growth inhibition examination

(Test method) Cell culture: Uterine-cervix-carcinoma HeLaS3 cell or melanoma A375 cell was cultured by Dulbecco's modified eagle medium (GIBCO (DMEM)) which added FCS 10%.

Compound evaluation: In DMEM, seeding of HeLaS3 cell or the A375 cell was carried out to 96 hole plate for cultured cells (made by IWAKI), and it was cultured overnight. The last concentration of DMSO was made the same at 0.1%, the DMSO solution of the evaluation compound was added by various concentration, and the color reaction by Alamar Blue (Biosource) estimated the proliferation of cells 48 hours after addition on the next day.

(Result) The compound (I) of this invention and (II) checked multiplication of the cancer cell good, and the IC50 value was below 1microM.

[moreover, the compound (I) of this invention and (II)] other cancer cells (non-small cell lung cancer (EKVX, HOP-92, NCI-H358, A-549, NCI-H460) --) A breast cancer (MDA-MB-231, MCF7), a prostatic cancer (PC-3), It had good proliferation-of-cells prevention activity similarly to a pancreatic cancer (MIA PaCa-2), colon cancer (WiDr), a renal cancer (A-498), gastric cancer (MKN28), vesical cancer (UC-14), and fibrosarcoma (HT-1080).

[0033]

Example 2 of an examination in vivo cancer growth inhibition examination

(Test method) 2x106 of A375 cell strain which is a melanoma were transplanted to the back hypodermic of a male Balb/c nude mouse. The evaluation compound was administered intravenously once per two-week day from the time of tumor capacity reaching [three] in 50-100mm. Moreover, the physiological saline was administered intravenously to the control group. For measurement of the diameter of a tumor, it measured temporally till the next day of the last administration using slide calipers. Tumor capacity was computed in the following formulas.

Tumor capacity (mm3) = 1 / 2x [minor axis (mm)] 2x major axis (mm)

(Result) In the exam, this invention compound (I) and (II) controlled cancer multiplication good, for example, the compound of work examples 4, 32, 101, 104, 122, 128, 151, and 153 showed 50% or more of multiplication control activity to the control group in 0.3 or 1mg/kg of administration.

this invention compound showed good cancer multiplication depressant action similarly in the animal model which transplanted other cancer cells (a prostatic cancer (PC-3) or non-small cell lung cancer (NCI-H358, A-549)).

[0034]

Example 3 of an examination Mouse single-dose toxicity study

(Test method) Single-dose administration of this invention compound was carried out to the Balb/C mouse by intravenous administration, and the existence of the example of death of a during [the observation period for two weeks] was examined.

(Result) The work examples 4, 6, 30, 32, 47, 66, 104, 114, 122, 128, 132, and 151 of this invention In 3mg [/kg] single-dose administration, the example of death all did not have the compound of 153, 155, 156, 157, 163, and 168. On the other hand in 3mg [/kg] single-dose administration, as for earlier literature Khim.Pharm.Zh., 32 (6), KP-1 that were indicated by 10-11 (1998), and KP-3, the example of all [in two examples] died, respectively. Therefore, it was shown that this invention compound has low toxicity as compared with an earlier literature compound.

Therefore, it was shown that it is useful as a treating agent of cancer which this invention compound (I) and (II) have good antitumor activity to two or more cancer types, and has a good profile from moreover it being low toxicity.

[0035]

The medicine constituent of this invention can be prepared by one sort of the compound shown by a general formula (I) or (II) or two sorts or more, and the method usually used using the carriers (the carrier for drugs, an excipient, etc.) which are usually used in the field for the time being, and which are permitted pharmaceutically. Administration may be which form of the parenteral administration by injections, such as internal use by a tablet, a pill, a capsule, the granule, powder, liquid medicine, inhalations, etc. or intravenous injection, and intramuscular injection, suppositories, ophthalmic solutions, an ophthalmic ointment, the liquid medicine for transderma, an ointment, the patches for transderma, permucosal liquid medicine, permucosal patches, etc.

A tablet, powder, a granule, etc. are used as a solid constituent for internal use by this invention. In such a solid constituent **, one, or the active substance beyond it is mixed with at least one inactivity

excipient, for example, milk sugar, a mannitol, grape sugar, hydroxypropylcellulose, a microcrystal cellulose, a starch, a polyvinylpyrrolidone, magnesium aluminometasilicate, etc. The constituent may contain disintegrator, such as lubricant, such as an inactivity additive agent, for example, magnesium stearate etc., and carboxy-methyl-starch sodium, and a solubilizing agent according to a conventional method. You may carry out the film of a tablet or the pill by sugar-coating, stomach solubility, or an enteric coating agent as occasion demands.

The liquid constituent for internal use contains the inactivity solvent generally used, for example, purified water, and ethanol including an emulsion, liquid medicine, suspension, syrups, elixirs, etc. which are permitted in drugs. This constituent may contain a solubilizer, a wetting agent, an auxiliary material like a suspending agent, a sweetening agent, corrigent, the aromatic, and the preservative in addition to an inactivity solvent.

[0036]

As injections for parenteral administration, sterile water or non-aqueous liquid medicine, suspension, and an emulsion are contained. As a water solvent, distilled water for injection and a physiological saline are contained, for example. As a non-aqueous solvent, there are propylene glycol, a polyethylene glycol, vegetable oil like olive oil, alcohols like ethanol, polysorbate 80 (brand name), etc., for example. Such a constituent may also contain an isotonizing agent, a preservative, a wetting agent, an emulsifier, a dispersing agent, a stabilizing agent, and a solubilizing agent further. These are sanitized by the combination or radiation of filtration and a fungicide which lets for example, a bacteria suspension filter pass. Moreover, these manufacture a sterile solid constituent, and they can also use it for non-bacterial water or the sterile solvent for injection before use, dissolving and suspending it in it.

Usually, when 50mg/kg of doses on the 1st are preferably administered intravenously in 0.01-30mg/kg from about 0.001 in internal use, the dose on the 1st is 10mg/kg from about 0.0001,

Preferably, kg is suitable respectively in 3mg /from about 0.001, and this is prescribed for the patient in 1 time per or two or more steps day. A dose is suitably determined according to each case in consideration of condition, age, sex, etc.

[0037]

[Example]

Based on a work example, this invention is explained still in detail hereafter. this invention compound is not limited to a compound given in the following work example at all. In addition, the example of manufacture of the raw material compound of this invention compound is shown in the example of reference.

Example 1 of reference: Saturated ammonia water (17ml) and Raney nickel (3.0g) were added to the ethanol (50ml) solution of the 3-cyano 2-(dimethylamino) pyridine (2.45g), and it agitated at the room temperature under the hydrogen atmosphere of breath pressure for 8 hours. The catalyst was ****(ed) after 760ml of hydrogen absorption. Mother liquor was condensed and the yellow oil-like 3-(aminomethyl)-2-(dimethylamino) pyridine (2.61g) was obtained.

Example 2 of reference: Several drops of strong sulfuric acid was added to the acetic anhydride (100ml) solution of 2-chloro 3-[(2-methoxy ethyl) amino]-1 and 4-naphtoquinone (33g), and it agitated at 45 degrees C for 1 hour. Ethanol (100ml) was added to reaction mixture, and the superfluous acetic anhydride was esterificated. Ethyl acetate was added after radiationnal cooling and it dried with anhydrous sodium sulfate after washing with water and saturation saline solution. The solvent was distilled off, the residue was crystallized from diethylether and N-(3-chloro 1, 4-dihydro1, 4-dioxo 2-naphtha RENIRU)-N-(2-methoxy ethyl) acetamido (29g) of yellow powder was obtained.

[0038]

Example 3 of reference: 2-methoxy ethylamine (0.8ml) was added to the benzene (20ml) solution of N-(3-chloro 1, 4-dihydro1, 4-dioxo 2-naphtha RENIRU) acetamido (1.0g), and it agitated under the room temperature for 1 hour. Water was added to reaction mixture and chloroform extracted. The organic layer was dried with anhydrous sodium sulfate after washing with water and saturation saline solution. The solvent was distilled off, recrystallization of the residue was carried out from ethyl acetate, and N-[3-(2-methoxy ethyl) amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU] acetamido (0.87g) of red powder was obtained.

Example 4 of reference: 2-(aminomethyl) pyrazine (3.2g) and diisopropyl ethylamine (5.8ml) were added to the benzene (90ml) solution of 2, 3-dichloro 1, 4-dihydro1, and 4-dioxo naphthalene (3.0g), and it agitated under the room temperature for 8 hours. The solid which added water to reaction mixture and deposited was ****(ed), and ethyl acetate extracted filtrate. The organic layer was dried with anhydrous sodium sulfate after washing with water and saturation saline solution. Silica gel column chromatography (eluted under chloroform) refined the residue after distilling off a solvent, and 2-chloro [of brown powder] 1, 4-dihydro1, and 4-dioxo 3-[(2-pyrazinyl methyl) amino] naphthalene (0.23g) was obtained.

[0039]

Example 5 of reference: Chlorination 2-chloro acetyl (3.3ml) was added to 1 of 2-chloro 1, 4-dihydro3-

methylamino 1, and 4-dioxo naphthalene (2.2g), and 4-dioxane (30ml) solution, and it agitated under flowing back for 14 hours. The solvent was distilled off after cooling reaction mixture radiationally. The solid which added ethanol to the residue and deposited was ****(ed). The obtained solid was recrystallized from ethanol and 2-chloro N-(3-chloro 1, 4-dihydro1, 4-dioxo 2-naphtha RENIRU)-N-methyl acetamido (2.6g) of yellow powder was obtained.

Example 6 of reference: NaH (440mg) was added to the DMF (20ml) solution of the 2-oxo-piperidine (1.0g) 60%, and it agitated for 30 minutes at the room temperature. This solution was added to the DMF (150ml) solution of 2, 3-dichloro 1, 4-dihydro1, and 4-dioxo naphthalene (6.9g) at a stretch, and it agitated at the room temperature for 17 hours. Reaction mixture was opened in saturated ammonia water, the depositing solid was ****(ed), and ethyl acetate extracted filtrate. The organic layer was dried with anhydrous sodium sulfate after washing with water and saturation saline solution. Silica gel column chromatography (eluted with ethyl acetate hexane 1:10 solution) refined the residue after distilling off a solvent, and 2-chloro [of brown powder] 1, 4-dihydro1, and 4-dioxo 3-(2-oxo-piperidino) naphthalene (0.49g) was obtained.

[0040]

The compound of the example 14 of reference which shows the compound of the examples 11-13 of reference which show the compound of the example 10 of reference which shows the compound of the examples 7-9 of reference shown in Table 1 in Table 2 like the example 2 of reference like the example 1 of reference in Table 2 like the example 3 of reference in Table 2 like the example 5 of reference was obtained, respectively.

[0041]

Work example 1: 2M sodium hydroxide aqueous solution (0.9ml) was added to the ethanol (10ml) solution of N-[3-(2-methoxy ethyl) amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU] acetamido (0.5g), and it agitated for 15 minutes under the room temperature. Water was added to reaction mixture and ethyl acetate extracted. The organic layer was dried with anhydrous sodium sulfate after washing with water and saturation saline solution. The solvent was distilled off, the residue was washed in **** and ethanol, and 1-(2-methoxy ethyl)-2-methyl [of light orange powder] 4, 9-dihydro4, and 9-dioxo 1H-[2 and 3-naphth d] imidazole (0.58g) was obtained.

Work example 2: Benzylamine (0.5ml) was added to the benzene (15ml) solution of N-(3-chloro 1, 4-dihydro1, 4-dioxo 2-naphtha RENIRU)-N-(2-methoxy ethyl) acetamido (0.5g), and it agitated at the room temperature for 4 hours. Ethyl acetate was added to reaction mixture and it dried with sulphuric anhydride magnesium after washing with water and saturation saline solution. The solvent was distilled off, the residue was crystallized from ethyl acetate hexane, and N-(3-benzylamino 1, 4-dihydro1, 4-dioxo 2-naphtha RENIRU)-N-(2-methoxy ethyl) acetamido (0.51g) of red powder was obtained.

[0042]

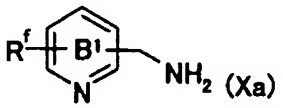
Work example 3: It is 3-chloro perbenzoic acid (0.6g) 80% to the dichloromethane (20ml) solution of N-(2-methoxy ethyl)-N-[3-(3-pyridyl methyl) amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU] acetamido (0.95g). In addition, it agitated at the room temperature for 18 hours. The saturation sodium bicarbonate aqueous solution was added to reaction mixture, and it extracted in dichloromethane. The organic layer was dried with anhydrous sodium sulfate after washing with water and saturation saline solution. Solvent Distill off and silica gel column chromatography (eluted with 10:1:0.chloroform methanol saturated ammonia water 1 solution) refines a residue. 3-[({3-[N-acetyl N-(2-methoxy ethyl)] amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU} amino) methyl] pyridine of a brown amorphous-like solid 1-oxide (0.84g) was obtained.

Work example 4: [the ethanol (30ml) solution of chlorination 1-(2-methoxy ethyl)-2-methyl 3-(4-pyridyl methyl)-4, 9-dihydro4, and 9-dioxo 1H-[2 and 3-naphth d] imidazole 3-IUMU a little salt acid chloride (1.1g)] 1M sodium hydroxide aqueous solution (5.0ml) In addition, it agitated for 30 minutes at the room temperature. Water was added to reaction mixture and ethyl acetate extracted. The organic layer was dried with sulphuric anhydride magnesium after washing with water and saturation saline solution. The solvent was distilled off and silica gel column chromatography (fraction A: eluted in elution and fraction B:ethyl acetate with ethyl acetate hexane 1:1 solution) refined the residue. Fraction A was crystallized from diethylether and N-[3-(2-methoxy ethyl) amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU]-N-(4-pyridyl methyl) acetamido (0.2g) of red powder was obtained. In addition, it is although Fraction B was crystallized from ethyl acetate and yellow powder (0.31g) was obtained, This was the same compound as N-(2-methoxy ethyl)-N-[3-(4-pyridyl methyl) amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU] acetamido of after-mentioned work-example 32 description.

[0043]

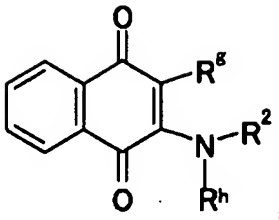
Example A of manufacture: N-[3-(2-hydroxyethyl) amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU]-N-methyl acetamido (0.4g) After carrying out a suspension to ethanol (3ml), 4M hydrogen chloride / ethyl acetate solution (3ml) was added, and it agitated at 45 degrees C for 1 hour. **** and ethyl acetate washed the produced precipitation after radiationnal cooling. The obtained solid was recrystallized from ethanol ethyl acetate, and chlorination 1-(2-hydroxyethyl)-2 in end of non-color

powder, 3-dimethyl 4; 9-dihydro4, and 9-dioxo 1H-[2 and 3-naphth d] imidazole 3-IUMU (0.28g) was obtained.
work example 5: the same method as the example A of manufacture -- N-(2-methoxy ethyl)-[acetamido / (0.49g) / N-{3-[(2-methoxy 3-pyridyl) methyl] amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU}] The chlorination 1-(2-hydroxy 3-pyridyl) methyl 3-(2-methoxy ethyl)-2-methyl 4 of brown powder, 9-dihydro4, and 9-dioxo 1H-[2 and 3-naphth d] imidazole 3-IUMU (0.39g) It obtained.
[0044]
Work example 6: They are 4M hydrogen chloride / ethyl acetate solution (10ml) to the ethanol (10ml) solution of N-{3-[(6-chloro 3-pyridyl) methyl] amino 1, 4-dihydro1, and 4-dioxo 2-naphtha RENIRU}-N-(2-methoxy ethyl) acetamido (0.8g). In addition, it agitated for one day at the room temperature. Solvent **** and ethyl acetate wash a residue after distilling off. The chlorination 1-[(6-chloro 3-pyridyl) methyl]-3-(2-methoxy ethyl)-2-methyl 4 of thin yellow powder, 9-dioxo 4, and 9-dihydro1H-[2 and 3-naphth d] imidazole 3-IUMU (0.82g) were obtained.
work example 7: They are 2M dimethyl amine / tetrahydrofuran solution (3.0ml) to the tetrahydrofuran (30ml) solution of 2-chloro N-[1, 4-dihydro3-(2-methoxy ethyl) amino 1, and 4-dioxo 2-naphtha RENIRU]-N-methyl acetamido (0.5g). In addition, it agitated at the room temperature for 18 hours. Water was added to reaction mixture and ethyl acetate extracted. The organic layer was dried with sulphuric anhydride magnesium after washing with water and saturation saline solution. The residue was crystallized from ethanol after distilling off a solvent, and N-[1, 4-dihydro3-(2-methoxy ethyl) amino 1, and 4-dioxo 2-naphtha RENIRU]-N-methyl 2-(dimethylamino) acetamido (0.19g) of brown powder was obtained.
The work-example compound of the description was obtained to the after-mentioned tables 3-17 like the above-mentioned work examples 1-5 or the example A of manufacture.
The constitutional formula and physicochemical character of a work-example compound are shown in the after-mentioned tables 1-2 in Tables 3-17 at the row of the example compound of reference, respectively. Moreover, almost like a method given in said work example or a manufacturing method, the compound [thing mentioned above / Tables 18-23 / a compound / a chemical structure type] applies some obvious strange method to a person skilled in the art at them, or is manufactured easily.
[0045]
the cable address in front -- Ex:work-example number Example number of Ref:reference; (in addition -- the inside of front, and "A")
the example A of manufacture is shown -- Sy:manufacturing method; Co:compound number; Sal: -- salt; (a number shows the number of said work example and A shows said example A of manufacture, respectively -- the compound concerned -- said this work example -- moreover)
The same method as the example of ****** [having manufactured] it is shown -- Dat:physicochemical character; Do not do -:existence of.; (F:FAB-MS (M)+; F':FAB-MS (M)-; F+:FAB-MS+(M+H); F-:FAB-MS-(M-H); E:EI-MS(M)+;) characteristic peak deltappm of N1:1 H-NMR (DMSO-d6, TMS internal standard); i-Pr: -- isopropyl; c-Pr:cyclo propyl; Ad:1-adamanthyl; Ac: -- acetyl; Bn: -- benzyl; Pipe; -- piperidino; Morp; -- morpholino; Py2;2-pyridyl; Py3;3-pyridyl; Py4;4-pyridyl; Th;2-thienyl; Fu;2-furil; Thf;2-tetrahydrofuranyl; Pyr;2-pyrazinyl; 5-MePyr;5-methyl 2-pyrazinyl; Pym;4-pyrimidinyl; Qu;3-quinolyl; Dio;4-benzodioxolyl; Im;4-imidazolyl; Bim;2-benzoimidazolyl; -- and -- In;2-India Lil is shown, respectively. In addition, the number in front of a substituent shows a substitution position, for example, is 3 and 4-Cl. : It is shown that -Cl replaces by the 3rd place and the 4th place, respectively.
[0046]
[Table 1]



Ref	B^1	$-R^f$	Dat	Ref	B^1	$-R^f$	Dat
1	Py3	2-NMe_2	F+: 152	8	Py4	2-NMe_2	F+: 152
7	Py3	6-NMe_2	F+: 152	9	Py3	2-OMe	E: 138

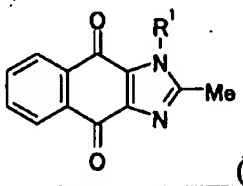
[0047]
[Table 2]



(IVa) or (VIa) or (VIIIa)

Ref	-R^g	-R^h	R^2	Dat
2	-Cl	-Ac	-$(CH_2)_2OMe$	N1: 1.88(3H,s), 2.99(3H,s), 3.3-3.9(4H,m), 7.9-8.2(4H,m)
3	-NH-$(CH_2)_2OMe$	-Ac	-H	F+: 289
4	-Cl	-H	-CH_2Pyr	F': 299
5	-Cl	-$COCH_2Cl$	-Me	F: 298
6	-Cl	-$CO(CH_2)_4$-		F+: 290
10	-Cl	-Ac	-CH_2Pyr	F': 341
11	-NH-CH_2(Py3)	-Ac	-H	F+: 322
12	-NH-CH_2(Py4)	-Ac	-H	F+: 322
13	-NH-CH_2(Pyr)	-Ac	-H	F+: 323
14	-Cl	-$COCH_2OMe$	-Me	F+: 294

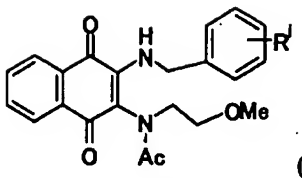
[0048]
[0049]
[Table 3]



(IIIa)

Ex.	-R^1	Dat	Ex.	-R^1	Dat
1	-$(CH_2)_2OMe$	F+: 271	9	-CH_2(Py4)	F+: 304
8	-CH_2(Py3)	F+: 304	10	-CH_2(Pyr)	F+: 305

[0050]
[Table 4]



(IIc)

Ex	-R[1]	Sy	Dat
2	-H	-	F+: 379 N1: 1.34(3H,br), 3.06(3H,s), 3.1-3.8(4H,m), 4.5-4.8(2H,m), 7.2-7.4(5H,m), 7.77(1H,dt), 7.85(1H,dt), 7.93(1H,br), 7.98(1H,d), 8.03(1H,d)
11	2-Cl	2	F+: 413
12	3-Cl	2	F+: 413
13	4-Cl	2	F+: 413 N1: 1.39(3H,br), 3.06(3H,s), 3.1-3.4(2H,m), 3.4-3.5(1H,m), 3.6-3.9(1H,m), 4.5-4.8(2H,m), 7.27(2H,d), 7.38(2H,d), 7.7-8.1(4H,m)
14	3,4-Cl	2	F: 447
15	2-OMe	2	F+: 409
16	3-OMe	2	F+: 409
17	4-OMe	2	F+: 409
18	4-Ph	2	F+: 455
19	2-CN	2	F+: 404
20	3-CN	2	F+: 404
21	4-CN	2	F+: 404
22	4-SO_2NH_2	2	F+: 458
23	4-CF_3	2	F+: 447
24	4-F	2	F+: 397 N1: 1.40(3H,br), 3.06(3H,s), 3.1-3.6(3H,m), 3.79(1H,br), 4.5-4.8(2H,m), 7.1-7.2(2H,m), 7.2-7.5(2H,m), 7.7-8.2(4H,m)
25	4-Br	2	F+: 457, 459
26	3-CH_2NH_2	2	F+: 408
27	4-CH_2NH_2	2	F: 407
28	3-NO_2	2	F+: 424
29	4-NO_2	2	F+: 424 N1: 1.39(3H,br), 3.07(3H,s), 3.1-3.6(3H,m), 3.6-3.9(1H,m), 4.6-5.0(2H,m), 7.54(2H,d), 7.7-8.2(5H,m), 8.19(2H,d)

[0051]

CONTINUE

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